

PART I: THE SYNTHESIS OF C3 HETEROADAMANTYL CANNABINOIDS

PART II: THE SYNTHESIS OF C3 HETEROAROYL CANNABINOIDS

A DISSERTATION SUBMITTED TO THE GRADUATE DIVISION OF THE  
UNIVERSITY OF HAWAI'I AT MĀNOA IN PARTIAL FULFILLMENT OF THE  
REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

DECEMBER 2010

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## **ACKNOWLEDGEMENTS**

I would like to express sincere gratitude to my advisor, Professor Marcus A. Tius, for his valuable guidance. His enthusiasm for chemistry and dedication to scientific research has been a true inspiration.

I would like to thank all Tius group members, past and present (especially Dr. Cisco Bee, Dr. Buck Batson, Go Ogawa, William Bow and Dr. Craig Stewart), for their friendship, insight and support as well as Dr. Tom Smith and Dr. Tore Benneche.

I would also like to thank my committee members, Professor Thomas Hemscheidt, Professor Philip Williams, Professor Oscar Navarro and Professor Patricia Lorenzo for their time and wisdom. Thank you to Wesley Yoshida, Mike Burger and Dr. Walt Niemczura for their help in acquiring NMR and mass spec data. Thank you to Professor B.J. Chain for providing me with space in his lab and for giving me lots of helpful suggestions.

I would also like to thank Janice and her family, as well as my family in Canada.

Finally, I would like to thank Professor Marcus A. Tius for his financial support in the form of research assistantships as well as the Department of Chemistry of the University of Hawai‘i at Mānoa for support in the form of teaching assistantships.

## ABSTRACT

**Part I:** The total synthesis of fourteen C9 hydroxyhexahydrocannabinol analogs, with heteroadamantyl moieties incorporated into the aliphatic side chain at C3, is described. The key steps in the synthesis were the condensation of persilylated phloroglucinol with diacetates derived from nopinone, the TMSOTf mediated formation of the dihydropyran ring, selective triflation at C3, stereoselective reduction at C9, palladium catalyzed cyanation, and Suzuki cross coupling of a vinyl pinacol boronate. Binding affinities of the analogs towards the cannabinoid receptors CB1 and CB2 were determined by *in vitro* assays. All analogs showed at least micromolar affinity for the receptors, while the C9  $\beta$ -hydroxy 2-oxadamantyl analog had the highest affinity for CB2 ( $K_i = 18.5$  nM) and showed a slight preference for CB2 over CB1. Molecular modeling of the analogs showed that the presence of a carbonyl or methylene linker at C1' drastically increases the pharmacophoric space resulting in decreased binding affinity.

**PART II:** The total synthesis of nineteen  $\beta$ -hydroxyhexahydrocannabinol analogs, with heteroaroyl moieties introduced at C3, is described. The key steps in the synthesis were the carbonylative Stille between the aryl triflate and heteroaroyl stannanes, addition of heteroaroyl groups to the aromatic aldehyde, and protecting group removal with TMSBr. Binding affinities of the analogs towards the cannabinoid receptors CB1 and CB2 were determined by *in vitro* assays and all analogs showed at least micromolar affinity for the

receptors, with the 3-benzothiophene ( $K_i = 34.2$  nM), 3-trifluoromethylphenyl ( $K_i = 45.8$  nM) and 3-indole ( $K_i = 60.4$  nM) analogs being most potent.



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## List of Abbreviations

[ $\alpha$ ]	specific rotation
abn-CBD	abnormal cannabidiol
AIDS	acquired immunodeficiency syndrome
AAI	aminoalkylindole
app	apparent
aq	aqueous
br	broadened
Bu	butyl
BHT	2,6-di- <i>tert</i> -butyltoluene
cAMP	cyclic adenosine monophosphate
Calcd.	calculated
cat.	catalytic
°C	degrees Celsius
CB1	cannabinoid receptor 1
CB2	cannabinoid receptor 2
CBD	cannabidiol
clogP	calculated logP
cm <sup>-1</sup>	reciprocal centimeters
$\delta$	chemical shift (parts per million)
2D	two dimensional

### List of Abbreviations (Continued)

3D	three dimensional
d	doublet
dd	doublet of doublets
ddd	doublet of doublet of doublets
DIBAL	diisobutylaluminum hydride
dppf	1,1'-bis(diphenylphosphino)ferrocene
dt	doublet of triplets
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
ee	enantiomeric excess
EI	electron impact
ESI	electrospray ionization
Et	ethyl
EtOAc	ethyl acetate
g	gram(s)
GPR18	G-coupled protein receptor 18
GPR55	G-coupled protein receptor 55
h	hour(s)



### List of Abbreviations (Continued)

HEK293	human embryonic kidney 293 cells
HHC	hexahydrocannabinol
HPLC	high performance liquid chromatography
HR MS	high resolution mass spectrum
h $\nu$	photoirradiation
Hz	hertz
IC <sub>50</sub>	half maximal inhibitory concentration
IR	infrared
<i>i</i> -Pr	iso propyl
<i>J</i>	coupling constant
K <sub>i</sub>	dissociation constant
K <sub>i</sub> <sup>*</sup>	apparent dissociation constant
L	liter(s)
LAB	lithium aminoborohydride
LAPS	ligand assisted protein structure
LC	liquid chromatography
LDA	lithium diisopropylamide
m	multiplet
M	molar (concentration)
M <sup>+</sup>	molecular ion

### List of Abbreviations (Continued)

MALDI	matrix assisted laser desorption/ionization
Me	methyl
MeNO <sub>2</sub>	nitromethane
MeOH	methanol
MHz	megahertz
min	minute(s)
mm Hg	millimeters of mercury
mg	milligram(s)
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
μL	microliter(s)
MS	mass spectrometry; or molecular sieves
<i>m/z</i>	mass to charge ratio
<i>n</i> -BuLi	<i>n</i> -butyllithium
NAH	northern aliphatic hydroxyl
nm	nanometer(s)
nM	nanomolar
Nf	nonaflate
N	normal (concentration)

### List of Abbreviations (Continued)

N.A.	not available
NMDA	<i>N</i> -methyl-D-aspartic acid
NMR	nuclear magnetic resonance
NSB	non-specific binding
OAc	acetoxy
<i>p</i> -TsOH·H <sub>2</sub> O	<i>para</i> -toluenesulfonic acid monohydrate
Ph	phenyl
PhNTf <sub>2</sub>	<i>N</i> -phenylbistrifluoromethanesulfonimide
Pin	pinacolato
PMHS	polymethylhydrosiloxane
ppm	parts per million
pyr	pyridine
q	quartet
quant	quantitative
<i>R</i>	rectus
RT	room temperature
s	second(s); in NMR: singlet
<i>S</i>	sinister
SAH	southern aliphatic hydroxy
SAR	structure activity relationship(s)

### List of Abbreviations (Continued)

satd.	saturated
<i>t</i>	tertiary
TBAF	tetrabutylammonium fluoride
td	triplet of doublets
TEA	triethylamine
TES	triethylsilyl
TESCl	triethylsilyl chloride
Tf	triflate
THC	tetrahydrocannabinol
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TOF	time of flight
UV	ultraviolet
wt. %	weight percent

## **PART I**

### **THE SYNTHESIS OF C3 HETEROADAMANTYL CANNABINOIDS**

## 1 Introduction

### 1.1 Pharmacohistory of *Cannabis sativa* L.<sup>1,2</sup>

*Cannabis sativa* L. is one of the most extensively used plants throughout time by man for fiber, food, medicine and social and religious rituals. It is a fast growing herbaceous annual propagated by seed and exists as two varieties namely, indica and non indica. Hemp, *C. sativa* fiber, comes from the stem and is very durable and is used in the manufacturing of rope, clothing, paper and a variety of other items. The flowers are typically small and green, yellow or white in color. *C. sativa* also has very distinctive leaves which are arranged palmately in five, seven, nine or other odd saw-toothed leaflets.<sup>3</sup> The female plants' flowering tops are covered with glandular hairs that secrete a resin which becomes abundant late in the plant's development and is believed to prevent desiccation of the seeds and to protect them during the ripening period. The use of *C. sativa* as a drug varies widely around the world. The most popular drug products derived from the plant are marijuana and hashish oil. Marijuana consists of any part of the plant that has been dried and is typically smoked while hashish oil is the resin from the plant.

*C. sativa* has been used as a folk medicine in various cultures since ancient times.<sup>4</sup> One of the first recorded uses of *C. sativa* was from a Chinese treatise over 2000 years ago where *C. sativa* was mixed with wine as an anesthetic in surgery.<sup>5</sup> *C. sativa* has also been used externally as a poultice or a constituent of various ointments for swelling and bruises. The seeds have been crushed and used in food or drink to treat depression. *C.*

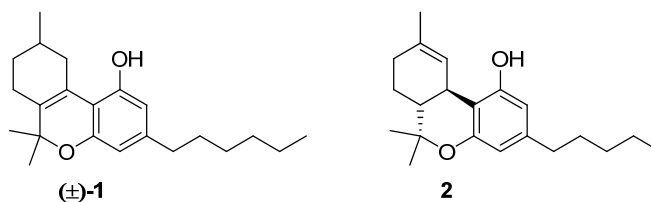
*sativa* has also been used to alleviate arthritis pain, chronic headaches, some psychosomatic disorders, as a spasmolytic, hypnotic, analgesic and to increase body resistance to severe physical stress.<sup>6</sup> Furthermore, *C. sativa* has been used as an appetite promoter, a general tonic to improve both the physical and mental state of the user and has also shown considerable success in the treatment of dysentery and cholera.

It wasn't until the 19<sup>th</sup> century that *C. sativa* was assimilated into the standard medical practice. An Irish scientist and physician, O'Shaughnessy, discovered that *C. sativa* preparations were very effective anti-vomiting agents.<sup>7</sup> Ethanolic extracts, or tinctures, of the resin were also given to patients to treat rheumatism, tetanus, rabies and infantile convulsions.

Even with all of *C. sativa*'s therapeutic potential its acceptance as a common medicine declined in the early 20<sup>th</sup> century. The main problem was the unavailability of the constituents of *C. sativa* in pure form and the lack of a reliable animal test that paralleled the activity in humans as well as the lack of controlled clinical experiments.

Adams<sup>8</sup> and Todd<sup>9</sup> renewed interest in *C. sativa* by identifying the basic structural features and synthesizing compounds with cannabimimetic activity in the 1940's.

Efficacy was reported for the most widely tested compound, racemic synhexyl (**1**), as an antidepressant and as a treatment for alcohol or opiate withdrawal but subsequent evaluations proved to be negative (**Figure 1.1.1**).



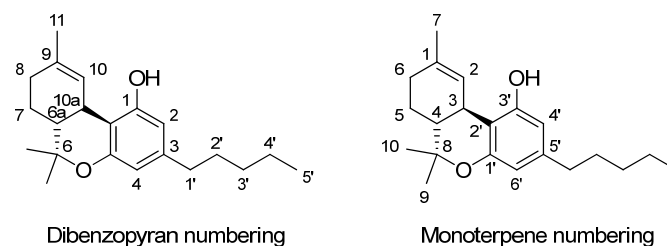
**Figure 1.1.1** Synhexyl and  $\Delta^9$ -THC.

In 1964, the isolation and structure elucidation of (-)- $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC, **2**), the primary psychoactive constituent of *C. sativa*, by Mechoulam and Gaoni of the Weizmann Institute of Science, opened the door for modern cannabinoid research.<sup>10</sup> Not long after this discovery, the United States Drug Enforcement Agency subjected *C. sativa* to strict controls under the Controlled Substances Act of 1970 which hampered the advancement of *C. sativa* as a potential widespread therapeutic. Even though *C. sativa* was considered a controlled substance, an enormous body of work has been published on the chemistry, pharmacology, behavioral effects and metabolism of natural and synthetic cannabinoids as well as efforts to probe the mechanisms responsible for the behavioral effects of cannabinoids.

## 1.2 Nomenclature of Cannabinoids

Two different numbering systems for cannabinoids with a dibenzopyran ring appear in the literature (**Figure 1.2.1**).<sup>11</sup> Most North American publications use the dibenzopyran numbering system while European publications use the monoterpenoid numbering system. In this dissertation, dibenzopyran ring nomenclature will be used for tricyclic cannabinoids.





**Figure 1.2.1** Numbering systems for cannabinoids.

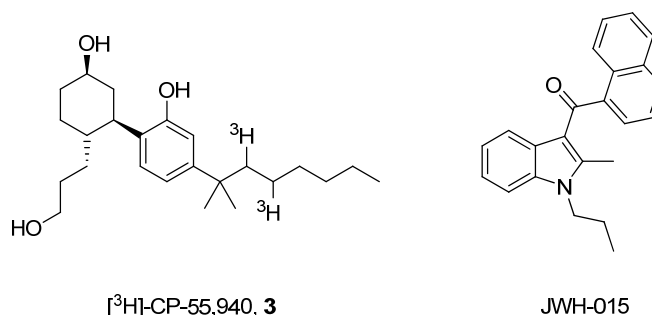
### 1.3 Cannabinoid Receptors

In the early 1980's it was speculated that cannabinoids produced their physiological and behavioral effects via non-specific interactions with cell membranes, instead of interacting with specific membrane bound receptors. It was later determined that the response of cannabimimetic drugs was consistent with receptor mediation rather than irreversible cytopathological change or increase in cell membrane fluidity induced by absorption of the highly lipophilic cannabinoids.<sup>12</sup> It was also found that cannabimimetic drugs cause inhibition of the enzyme adenylate cyclase, which is responsible for the synthesis of cyclic adenosine monophosphate (cAMP), resulting in low cAMP levels in neuronal cells. The phosphorylation of key enzymes and proteins in the cell is regulated by cAMP, but it is unclear how this is linked to the physiological and psychological effects of cannabimimetic drugs.

#### 1.3.1 CB1 Receptor

In 1988, Devane<sup>13</sup> and co-workers discovered the first cannabinoid receptor, CB1, through the use of ligand binding assays using tritium labeled [<sup>3</sup>H]-CP-55,940 (**3**) with

P<sub>2</sub>-membranes and synaptosomes from rat brain (**Figure 1.3.1**). From their work they determined that the receptor's mode of action was consistent with that of a second messenger membrane bound G-protein receptor inhibiting adenylate cyclase in a reversible, competitive, enantioselective and cell specific fashion and that it is more responsive to psychoactive cannabinoids than non-psychoactive cannabinoids. After the receptor is engaged, multiple intracellular transduction pathways are activated. Initially, it was thought that the cannabinoid receptors mainly activate the G protein which inhibits the enzyme adenylate cyclase, which results in the inability to produce a second messenger molecule of cAMP, and has a positive influence on inwardly rectifying potassium channels. It has also been shown that cannabinoids have other implications on various potassium ion channels, calcium channels, protein kinase A and C and many other systems.<sup>14</sup>



**Figure 1.3.1** Cannabinoid ligands [<sup>3</sup>H]-CP-55940 (**3**) and JWH-015.

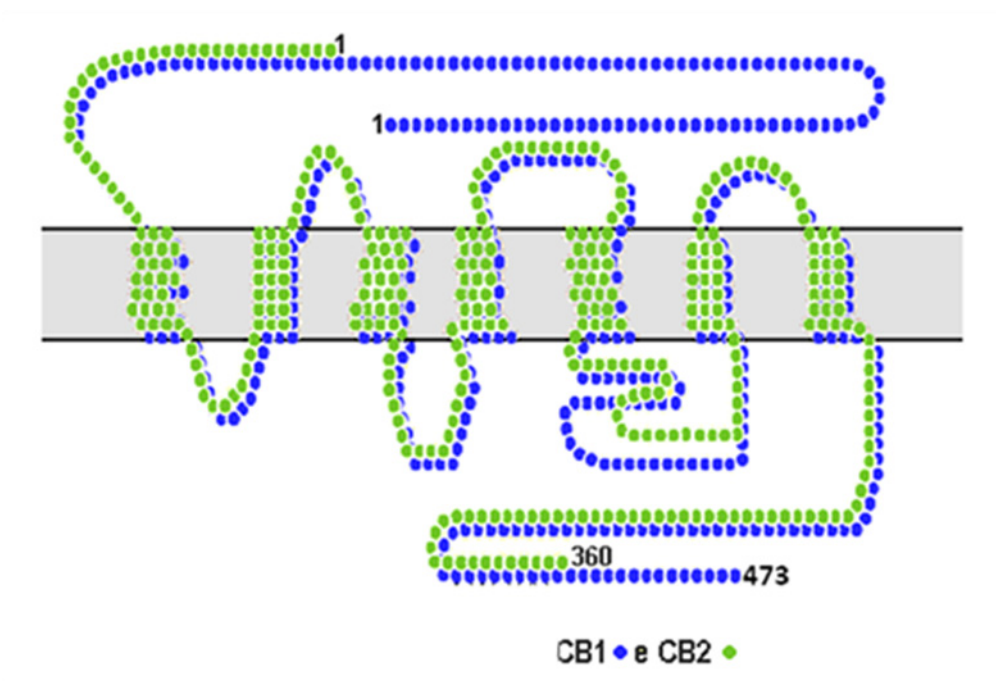
Autoradiographic techniques revealed that the CB1 receptor can be found throughout the brain and spinal cord, but that it is primarily concentrated in the basal ganglia, hippocampus and cerebellum. The receptors can also be found in the lungs, liver and

kidneys but are also expressed on the pituitary gland, thyroid gland and most likely the adrenal gland. CB1 is also expressed on cells relating to metabolism, such as fat, muscle and liver cells, and in the digestive tract and can also be found on sperm and ovarian cells.<sup>15</sup>

Activation of the CB1 receptor has various functions throughout the body. In the liver, activation of the receptor is known to increase de novo lipogenesis, inhibit sympathetic innervation of blood vessels and contribute to the suppression of the neurogenic vasopressor response in septic shock. Activation of the CB1 receptor in the cardiovascular system contributes to hemorrhagic and endotoxin induced hypotension.<sup>16</sup> Activation of CB1 results in analgesic activity as well.

### **1.3.2 CB2 Receptor**

Through the use of polymerase chain reaction (PCR) techniques on DNA prepared from human promyelocytic leukaemic line (HL60) Munro<sup>17</sup> and co-workers at Cambridge discovered the second cannabinoid receptor, CB2, in 1993. This new receptor was shown to have significant homology with CB1 with 44% amino acid similarity overall and 68% amino acid similarity in the transmembrane regions. The CB2 receptor is comprised of 360 amino acids while CB1 is considerably longer with 473 (**Figure 1.3.2**).<sup>18</sup> The sequence of amino acids across human and rodent species is not as highly conserved in the CB2 receptor (only 81% amino acid homology) as it is in the CB1 receptor (97-99% amino acid homology).



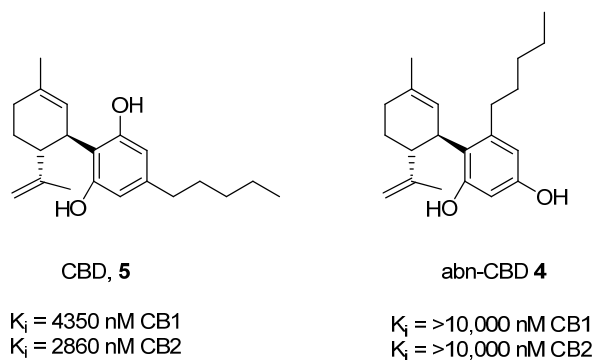
**Figure 1.3.2** Structures of the CB1 and CB2 receptors shown with the membrane.<sup>18</sup>

The CB2 receptors are largely found throughout the peripheral tissues, such as the immune system (spleen, tonsils and thymus gland) with the greatest density in the T cells of the spleen. It has recently been reported that the expression of CB2 is induced within the lumbar spinal cord in chronic pain models associated with peripheral nerve injury. The appearance of CB2 coincides with activated microglia (a type of glial cell that acts as the main form of active immune defense in the central nervous system).<sup>19</sup> Recent research has shown that CB2 receptors are also widely distributed throughout the brain where their role remains unclear, and in the gastrointestinal system where they modulate intestinal inflammatory response. CB2 receptor agonists make an attractive target for drug discovery since they lack the undesirable behavioral and psychoactive side effects

associated with activation of the CB1 receptor. CB2 agonist JWH-015 (**Figure 1.3.1**) has been shown to induce macrophages to remove native beta-amyloid protein from frozen human tissues.<sup>20</sup> This finding has importance in Alzheimer's research since it is known that patients suffering from this disease have buildups of beta-amyloid proteins known as senile plaques, which disrupt neural functioning. CB2 receptor agonists are potential therapeutic targets for the treatment of pain, inflammatory bowel diseases such as Crohn's,<sup>21</sup> ulcerative colitis<sup>22</sup> and a possible treatment of Alzheimer's.

### **1.3.3 Possible Non CB1/CB2 Receptors**

The existence of non-CB1/CB2 receptors has long been suspected due to the actions of compounds that produce cannabinoid-like effects on blood pressure and inflammation without activating CB1 or CB2. Abnormal cannabidiol (abn-CBD, **4**), a synthetic regioisomer of cannabidiol (CBD, **5**), is such a compound that has vasodilator effects, lowers blood pressure and induces cell migration and proliferation without psychoactive effects (**Figure 1.3.3**). Research has shown that the actions of **4** are mediated through a receptor other than CB1 and CB2. These observations suggest that the abn-CBD receptor is the orphan receptor GPR18, which has been shown to be a receptor for endogenous lipid neurotransmitters which in turn also bind to cannabinoid receptors. In time, GPR18 could also be termed a cannabinoid receptor.<sup>23</sup> Another orphan receptor, GPR55, is thought to be another potential cannabinoid receptor based on sequence homology at the binding site and its ability to respond to both exogenous and endogenous cannabinoid ligands.<sup>24</sup>

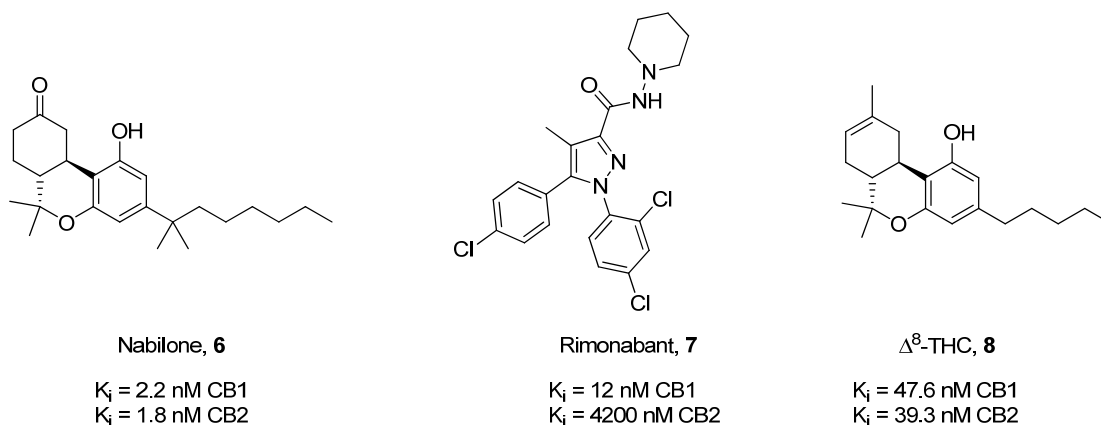


**Figure 1.3.3** Cannabidiol (CBD, **5**) and abnormal cannabidiol (abn-CBD, **4**).

#### 1.4 Therapeutic Potential of Cannabinoids and Synthetic Analogs

To date there have only been three cannabinoid receptor agonists approved for the treatment of specific ailments. (-)- $\Delta^9$ -THC has a broad pharmacological spectrum consisting of, inter alia, anticonvulsant, analgesic,<sup>25</sup> ocular hypotensive,<sup>26</sup> bronchodilator, and antiemetic effects in animals and humans. In spite of the potential of **2** and synthetic analogs thereof, there has been limited success in bringing such compounds to the drug market.

(-)- $\Delta^9$ -THC and the synthetic analog nabilone (**6**) have demonstrated safety and efficacy as oral antiemetics in cancer chemotherapy and are commercially available as Dronabinol (Unimed, Inc.) and Cesamet<sup>®</sup> (Eli Lilly and Company), respectively (**Figure 1.4.1**). (-)- $\Delta^8$ -THC has also been shown to be an effective antiemetic for children undergoing cancer chemotherapy albeit in much higher doses and with negligible side effects.<sup>27</sup>



**Figure 1.4.1** Therapeutic cannabinoids.

Solvay Pharmaceuticals is also marketing Marinol<sup>®</sup> (**2**) as a treatment for cachexia in AIDS patients.<sup>28</sup> Recently, nabilone (**6**) has also shown to be effective for the treatment of pain due to fibromyalgia<sup>29</sup> and for the treatment of nightmares associated with post-traumatic stress disorder.<sup>29</sup> In Canada, an oralmucosal spray consisting of a roughly equal parts mixture of **2** and cannabidiol **5** under the trade name Sativex was approved for the treatment of neuropathic pain associated with multiple sclerosis patients and cancer patients who showed persistent pain under maximal doses of opioid treatment.<sup>30</sup>

Sanofi-Aventis released CB1 antagonist rimonabant (Acomplia<sup>®</sup>, **7**) in 2006 to treat obesity.<sup>31</sup> Unfortunately, it was removed from the market just two years after its release due to its users experiencing anxiety and depression which in extreme cases led to suicide. Rimonabant has also shown promise as a smoking cessation aid.<sup>32</sup> Other potential uses are for the treatment of addictions such as cocaine<sup>33</sup> and ethanol,<sup>34</sup>

improvement of short-term memory<sup>35</sup> and blocking the psychoactive and cardiovascular effects<sup>36</sup> that are associated with **2**.

### 1.5 Cannabinoid Ligands and Structure Activity Relationship (SAR)

The synthesis of natural and synthetic cannabinoid enantiomeric pairs has made it possible to compare their pharmacological and biological activities. In most cases, the natural *trans*-(6a*R*, 10a*R*)-(-)-cannabinoids show significant activity while the antipode exhibits very little or no activity.<sup>37</sup> The high potency of the (-)-enantiomer is consistent with the existence of a specific receptor for cannabinoids. However, both enantiomers of **5** exhibit anticonvulsant activity which suggests that this activity results from nonspecific membrane interactions.<sup>38</sup>

Tentative rules for cannabimimetic activity were formulated by Mechoulam and Edery in 1973 based on pharmacological studies carried out after the primary active constituent in marijuana,  $\Delta^9$ -THC, was identified.<sup>39</sup> Both naturally occurring and synthetic cannabinoids generally follow these rules. The term cannabimimetic refers to ligands that produce human subjective effects in common with  $\Delta^9$ -THC or that produce  $\Delta^9$ -THC like activity in laboratory animals that parallels human activity.<sup>40</sup> To assess the psychoactive component of cannabinoids animal behavior is studied.<sup>41</sup> Some common behaviors resulting from the treatment of laboratory animals with cannabinoids are dog ataxia, spontaneous activity and hypothermia in rats and mice, overt behavior in Rhesus monkeys and baboons, drug discrimination in rodents, pigeons or monkeys and the



mouse ring test. It is not possible to quantify the extent of separation of psychoactive and other side effects from therapeutic based on these tests.

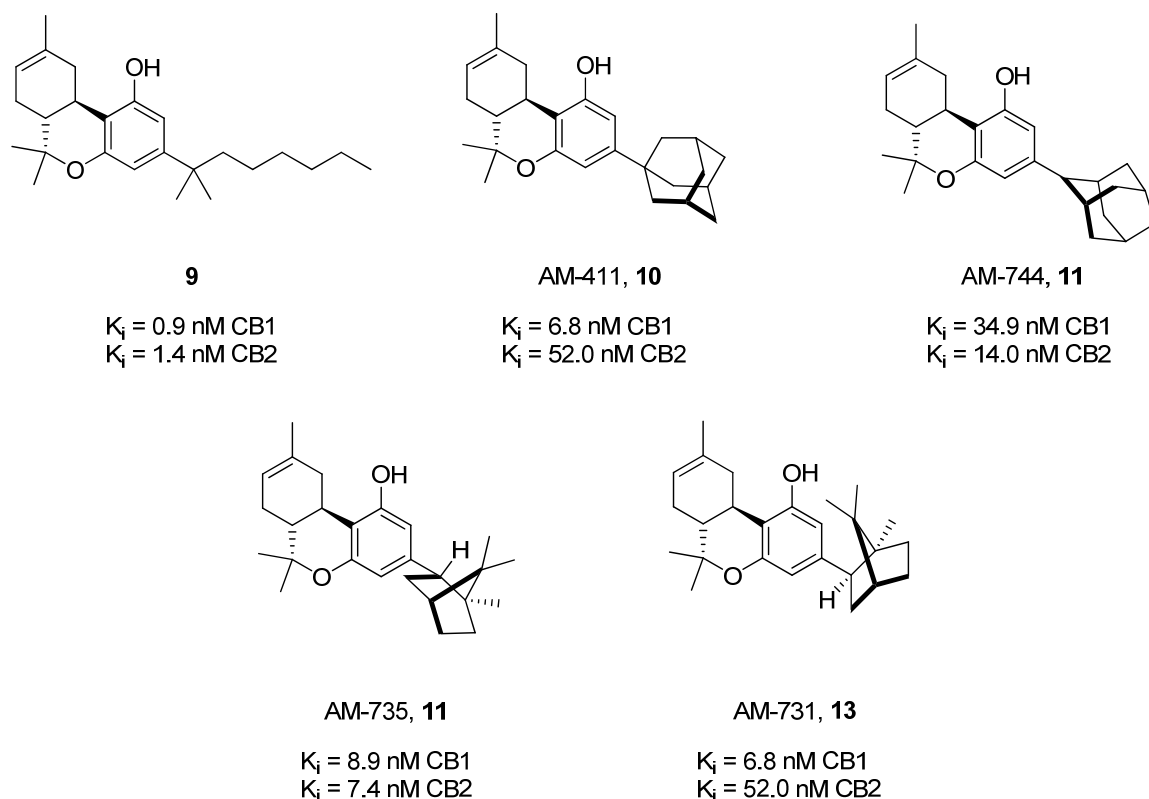
To date there have been five structurally diverse types of ligands that are classified as cannabinoids. Each class of ligands will be discussed briefly as well as their structure activity relationships.

### **1.5.1 Classical, Non-Classical and Hybrid Cannabinoids**

Classical cannabinoids are naturally occurring or synthetic cannabinoids that contain the tricyclic framework as seen in  $\Delta^9$ -THC. Considerable effort has been devoted to the SAR of these cannabinoids and three key pharmacophoric features have been discovered. The key pharmacophores are C9 of the cyclohexane ring as well as C1 and C3<sup>42</sup> of the aromatic ring.

The identity of the alkyl group at C3 is considered the dominant factor in determining cannabinergic potency. The presence of an alkyl side chain is a prerequisite for cannabimimetic activity. The alkyl chain must be at least as long as the *n*-pentyl chain found in  $\Delta^9$ -THC and a length of seven carbon atoms appears to be optimal. Activity is still observed if the C1' carbon is replaced by an oxygen, while activity increases with the presence of methyl groups at the 1'- or 2'-position. The most widely used side chain in synthetic cannabinoid analogs is the 1',1'-dimethylheptyl side chain.<sup>43</sup> Recently, it has been shown that groups as large as bornyl, isobornyl<sup>44</sup> and adamantyl<sup>45</sup> are still tolerated in both CB1 and CB2 binding sites. Furthermore, considerable receptor subtype

selectivity was observed depending on the relative orientation of the adamantyl or bornyl and isobornyl group with respect to the tricyclic nucleus (**Figure 1.5.1**).



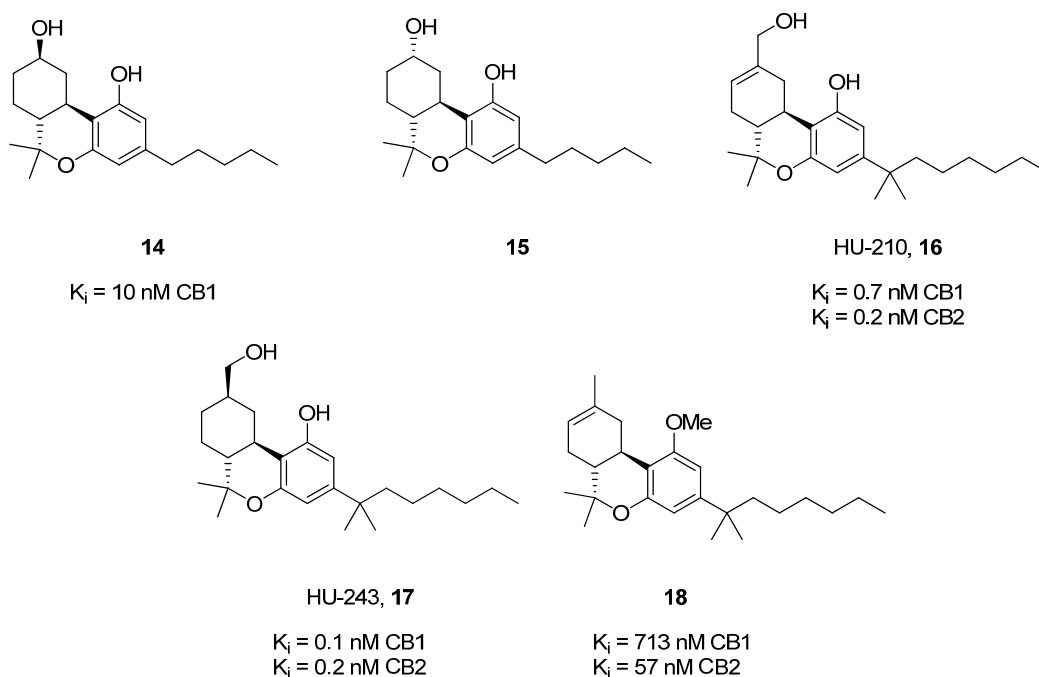
**Figure 1.5.1** C3 varied classical cannabinoids.

The  $\Delta^9$ - or  $\Delta^8$ -double bond is not important for activity. Substitution of the northern aliphatic hydroxy groups (NAH) for other groups such as a carbonyl,  $\beta$ -hydroxy or  $\beta$ -hydroxymethyl at C9 all lead to an increase in activity (**Figure 1.5.2**). The  $\alpha$ -isomers are still active but to a much lesser extent. The studies of Wilson and May using 9-nor-9 $\beta$ -hydroxyhexahydrocannabinol (**14**) and epimeric **15** led to research in the non-classical cannabinoid field (**Figure 1.5.2**). Both **14** and **15** produced cannabimimetic activity but

**15** exhibited enhanced analgesic activity in rodents, with potency equal to morphine.<sup>46</sup>

These results represented a significant step forward in the search for non-narcotic, potent analgesics structurally unrelated to morphine.

Structure activity relationships have also shown that one and only one phenolic hydroxy group is required to maintain cannabimimetic activity and the phenolic hydroxy at C1 has to be free or esterified.<sup>47</sup> Blocking of the hydroxyl group as an ether (**18**) leads to elimination of or considerable reduction of activity when compared to **9**.



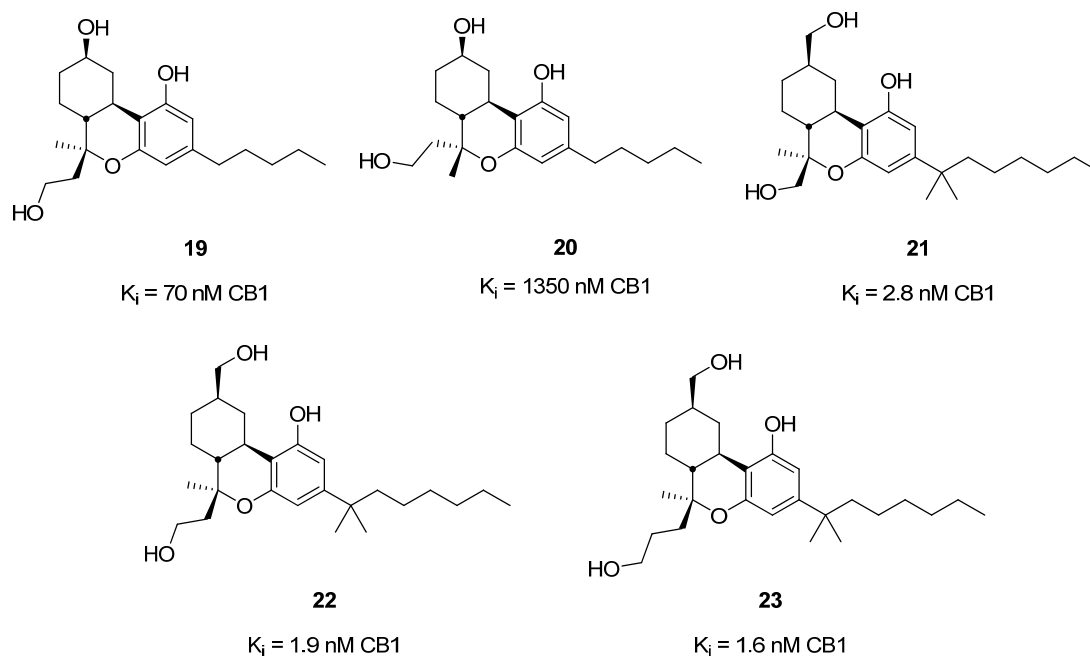
**Figure 1.5.2** C9 and C1 varied classical cannabinoids.

Most active cannabinoids contain the dihydrobenzopyran moiety with the *trans*-6a*R*, 10a*R* ring fusion to the aliphatic C ring; however, in some non-classical cannabinoids the

dihhydropyran ring is replaced by an aliphatic chain terminating in a hydroxyl group as seen in **3** (**Figure 1.3.1**). This functionality at C6 is termed the southern aliphatic hydroxy group (SAH). The SAH can also be a simple alkyl chain, have unsaturation, be halogenated or be incorporated into another ring, all of which modulate binding affinity. In an attempt to delineate the minimum structural requirements for hexahydrocannabinol (**15**) needed to induce analgesia, it was found that the dihydropyran ring was not necessary for activity.<sup>48</sup> A wide variety of these simplified analogs have been developed and in fact, tritiated non-classical cannabinoid [<sup>3</sup>H]-CP-55,940 (**3**) was used to identify the CB1 receptor in rat brain. Naturally occurring cannabinoid **5**, which lacks the dihydropyran ring, is completely devoid of cannabimimetic activity and most other major activity except for anticonvulsant activity.<sup>49</sup>

Hybrid cannabinoids were introduced by Tius *et al.* in 1994 when they prepared tricyclic cannabinoids **19** and **20** (**Figure 1.5.3**).<sup>50</sup> These hybrid cannabinoids incorporated all four key pharmacophores associated with classical and non-classical cannabinoids (NAH, SAH, C1 phenolic hydroxyl and C3 alkyl chain) while limiting the conformational mobility of the SAH bearing group. The  $\beta$ -hydroxyethyl compound **19** showed 20x higher affinity than **20**, demonstrating that the SAH-receptor interaction takes place on the  $\beta$ -face of the classical cannabinoid skeleton. Hybrids of the highly potent cannabinoids HU-243 (**17**) and CP-55,940 were also prepared by varying the length of the southern  $\beta$ -hydroxyalkyl chain from one to three methylene units.<sup>51</sup> As expected, replacing the C9 hydroxy group and the *n*-pentyl chain with  $\beta$ -hydroxymethyl and 1',1'-

dimethylheptyl groups respectively, greatly increased receptor affinity. However, varying the length of the southern  $\beta$ -hydroxyalkyl chain had minimal effect on the affinity. It was also observed that the presence of the new SAH in the HU-243/CP-55,940 hybrids (**21**, **22** and **23**) interferes with the optimal receptor interactions of the other pharmacophores resulting in compounds 40x less potent than the parent compound HU-243.

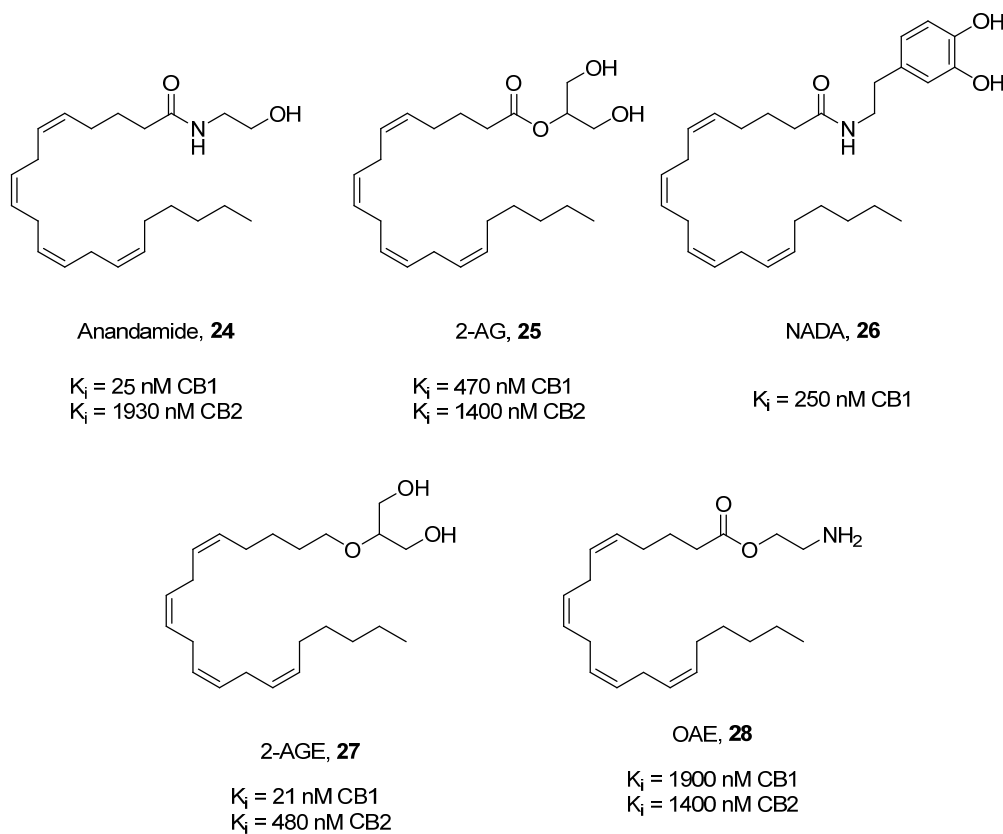


**Figure 1.5.3** Hybrid cannabinoids.

### 1.5.2 Endocannabinoids

With the discovery of the CB1 receptor the search for endogenous ligands, or endocannabinoids, began. The first such ligand, anandamide (**24**), was isolated from porcine brain in 1992 by Mechoulam and was shown to bind strongly to the CB1 receptor

but only weakly to CB2 (**Figure 1.5.4**).<sup>52</sup> 2-Arachidonyl glycerol (2-AG, **25**), the first endogenous ligand to be found outside of the brain, binds both receptors with similar affinity, acting as a full agonist at both.<sup>53</sup> N-Arachidonyl-dopamine (NADA, **26**) was discovered in 2000 and preferentially binds to CB1.<sup>54</sup> 2-Arachidonyl glyceryl ether (2-AGE, **27**) was also isolated from porcine brain in 2001 and was shown to bind strongly to CB1 causing sedation, hypothermia, intestinal mobility and mild antinociception in mice.<sup>55</sup> Lastly, O-arachidonyl-ethanolamine (OAE, **28**) was discovered in 2002 in the brain and in slightly higher concentrations in the peripheral tissues.<sup>56</sup>



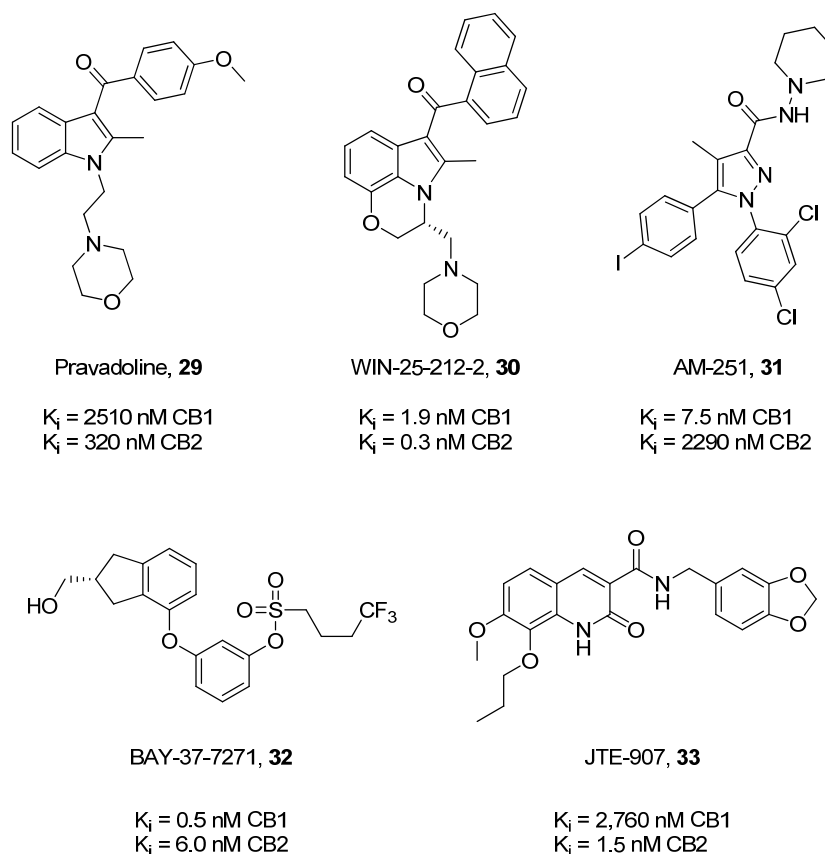
**Figure 1.5.4** Endocannabinoids.

It has been shown that conservation of the ethanolamide end group is not necessary for receptor binding affinity and that elongation and branching of the end group can increase binding affinity.<sup>57</sup> The four *cis*-olefins are the key feature in maintaining high activity, although replacement of the hydrophobic tail is tolerated as is in the case of  $\Delta^9$ -THC. Conversion of the *n*-pentyl tail to dimethylheptyl has been shown to improve binding. Through molecular modeling experiments it has been suggested that the endocannabinoids interact with the receptor in a similar fashion to the bicyclic and tricyclic cannabinoids.

### 1.5.3 Aminoalkylindoles, 1,5-Diarylpyrazoles and Miscellaneous Cannabinoids

Sterling-Winthrop Co. stumbled upon the aminoalkylindole (AAI) cannabinoid ligands in the 1990's while they were developing anti-inflammatory agents. Pravadoline (WIN-48098, **29**) was found to exhibit unexpectedly strong analgesic effects and these effects were not blocked by opioid antagonists (**Figure 1.5.5**).<sup>58</sup> Eventually it was discovered that pravadoline represented the first compound in the class of AAIs. (+)-WIN-55212-2 (**30**) was another compound that showed little promise as an anti-inflammatory drug, but it did prove to be a very potent cannabimimetic displaying the full range of effects in behavioral studies. The tritiated analog is now widely used as a radioligand standard in SAR studies. The most potent AAIs contain an indole ring system, a tertiary amine moiety and a naphthoyl or aroyl group. The carbonyl oxygen of AAIs was shown to be unnecessary for cannabinoid receptor affinity and activity. Also, the morpholino ring can be replaced by an alkyl chain without loss of CB1 affinity or efficacy. The naphthoyl

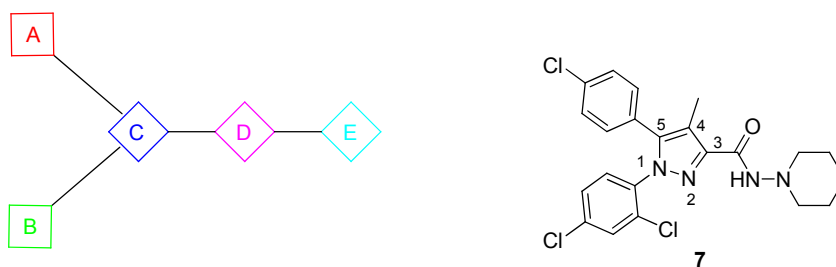
moiety appears to be the preferred aromatic moiety and shows increased binding affinity compared to the *p*-methoxybenzoyl present in **29**, supporting the hypothesis that aromatic stacking interactions are important for interacting with the CB1 and CB2 receptors.<sup>59</sup>



**Figure 1.5.5** 1, 5-Diarylpyrazoles, aminoalkylindoles and miscellaneous cannabinoids.

In 1994 Sanofi-Aventis introduced the first selective cannabinoid antagonist, SR-141716 (**7**), belonging to a family of 1,5-diarylpyrazoles.<sup>60</sup> Most CB1 antagonists to date closely resemble **7** and contain a cyclic core, C, substituted by two aromatic moieties, A and B, and a hydrogen bond acceptor, D, with a lipophilic sidechain E (**Figure 1.5.6**).



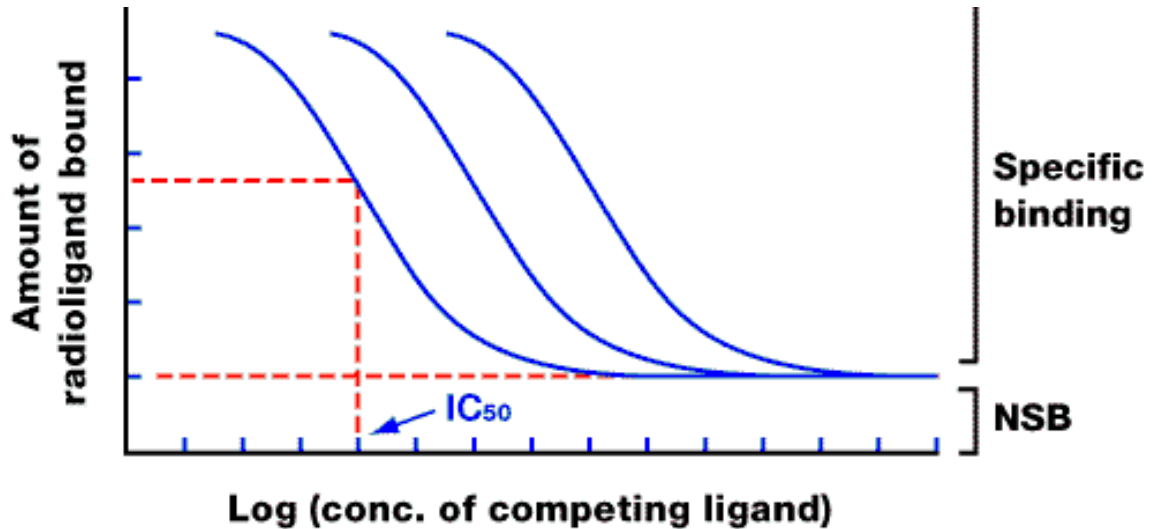


**Figure 1.5.6** 1,5-Diarylpyrazole skeleton system.

SAR studies found that a *para*-substituted phenyl A ring is required for optimal binding affinity and that the A ring is involved in receptor recognition. The *para*-substituent can be chlorine, bromine or iodine as well as an alkyl chain but iodine analogs have the highest affinity. A 2,4-dichloro substituted B ring ensures high activity and receptor affinity while any deviation from this is detrimental.<sup>61</sup> Having a cyclic lipophilic E moiety is also favorable while replacement with alkyl amides, ethers, ketones, alcohols or alkenes result in decreased activity. It is interesting to note that replacement of the cyclic lipophilic moiety with a pentyl or heptyl chain gives the compounds agonistic properties. Studies have also shown that absence of the carboxamide oxygen, or hydrogen bond acceptor D, results in decreased affinity. Furthermore, the presence of the carboxamide oxygen confers the inverse agonist properties while compounds devoid of the oxygen are neutral antagonists which support the hypothesis that the carboxamide oxygen forms a key hydrogen bond inside of the CB1 receptor. Other examples of cannabinoid ligands include the diarylether sulfonyl ester BAY-37-7271 (**32**) and JTE-907 (**33**) (**Figure 1.5.5**).



to a non-linear regression curve resulting in a half maximal inhibitory concentration ( $IC_{50}$ ) curve. The concentration at which half of the substrate is displaced is determined to be the  $IC_{50}$  value for the inhibitor (**Figure 1.6.2**).



**Figure 1.6.2** Typical  $IC_{50}$  curve.

Since  $IC_{50}$  values are concentration dependent the values will vary between experiments.

The preferred value to report is the  $K_i$  value, or inhibition constant. The inhibition constant is an absolute value and independent of concentration which is more useful to the experimentalist. The  $K_i$  value is calculated using the Chang-Preusoff equation (**Equation 1**).<sup>64</sup>

$$K_i = IC_{50} / (1 + [S]/K_m) \quad (\text{Equation 1})$$

The Chang-Preusoff equation consists of the  $IC_{50}$  value determined for the inhibitor, concentration of the substrate  $[S]$  and the Michaelis-Menten constant for the substrate.

This equation may only be used when the substrate and inhibitor bind in a competitive manner. If the substrate and inhibitor bind in a non-competitive or allosteric manner a different equation must be used to determine the inhibition constant.

### **1.6.2 Ligand Assisted Protein Structure (LAPS)**

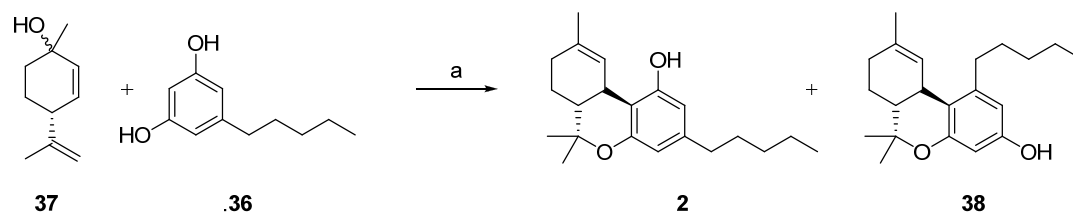
Ligand assisted protein structure (LAPS) is a recently developed technique combining molecular biology and mass spectroscopy focused proteomics. This method is advantageous since it determines which amino acid residues interact with the bound ligand inside the reactive site. Our collaborator, Professor Alexandros Makriyannis, uses this technique to help divulge information about the active binding site in the cannabinoid receptors, CB1 and CB2. This is accomplished by utilizing a cannabinoid ligand containing a reactive functional group (i.e.: azide, isothiocyanate, etc.) which can undergo a reaction inside the receptor resulting in a covalent bond. This adduct can then undergo partial enzymatic degradation and is analyzed using MALDI-TOF or MS/MS experiments. A determination of the orientation of the ligand inside the receptor can then be made based on the mass fragments.

## **1.7 Previous Synthetic Approaches to Cannabinoids and Analogs**

### **1.7.1 Approaches to $\Delta^9$ -THC and Analogs**

The most common procedure for preparing cannabinoids focuses on reactions of olivetol (**36**) with an appropriately functionalized monoterpene derivative such as **37**. The major drawback of this approach is the formation of a 1/1 mixture of regioisomers derived from

substitution at C2 and C4 of olivetol.<sup>65</sup> The byproduct, in which the hydroxyl and *n*-pentyl groups are transposed, is referred to as the “abnormal” cannabinoid (**38**) (Scheme 1.7.1).

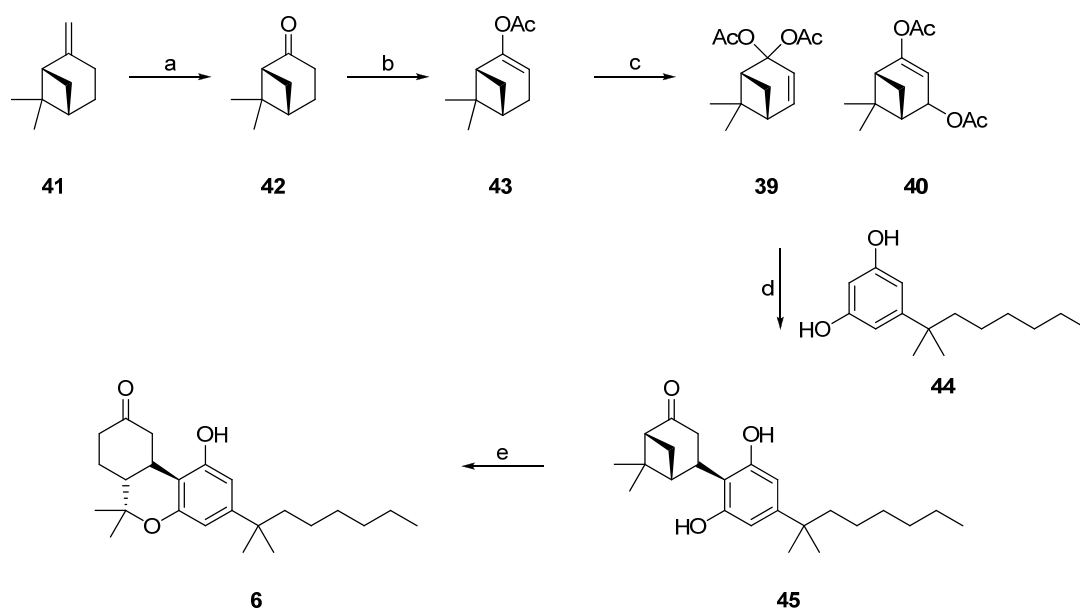


**Scheme 1.7.1** Reagents and conditions: (a) *p*-TsOH·H<sub>2</sub>O, CHCl<sub>3</sub> or PhH.

The “abnormal” cannabinoid byproduct can be suppressed when the resorcinol has a bulky substituent at C5 which presumably prevents attack at C4 due to sterics.<sup>66</sup>

Various chiral cyclic monoterpeneoids have been used to synthesize  $\Delta^9$ -THC including *cis*- and *trans*-*p*-mentha-2,8-dien-1-ol (**37**),<sup>67</sup> (+)-*trans*-2,3-epoxycarane,<sup>68</sup> (-)-*cis*- or (-)-*trans*-verbenol<sup>69</sup> and (+)-(1*R*,4*R*)-*p*-menth-2-ene-1,8-diol.<sup>70</sup> Of these, **37** and (+)-(1*R*,4*R*)-*p*-menth-2-ene-1,8-diol have the most synthetic utility. It should be noted that since the cationic condensations are promoted by Lewis acids, the regiochemical outcome is quite sensitive to reaction conditions. When strong protic acids are used in the condensation/cyclization reaction the thermodynamically more stable  $\Delta^8$ -THC is formed which requires additional steps to yield the desired  $\Delta^9$ -THC.<sup>71</sup> To get around the undesirable isomerization, the use of catalytic BF<sub>3</sub>·Et<sub>2</sub>O in the presence of MgSO<sub>4</sub> results in  $\Delta^9$ -THC as the major product.<sup>66</sup>

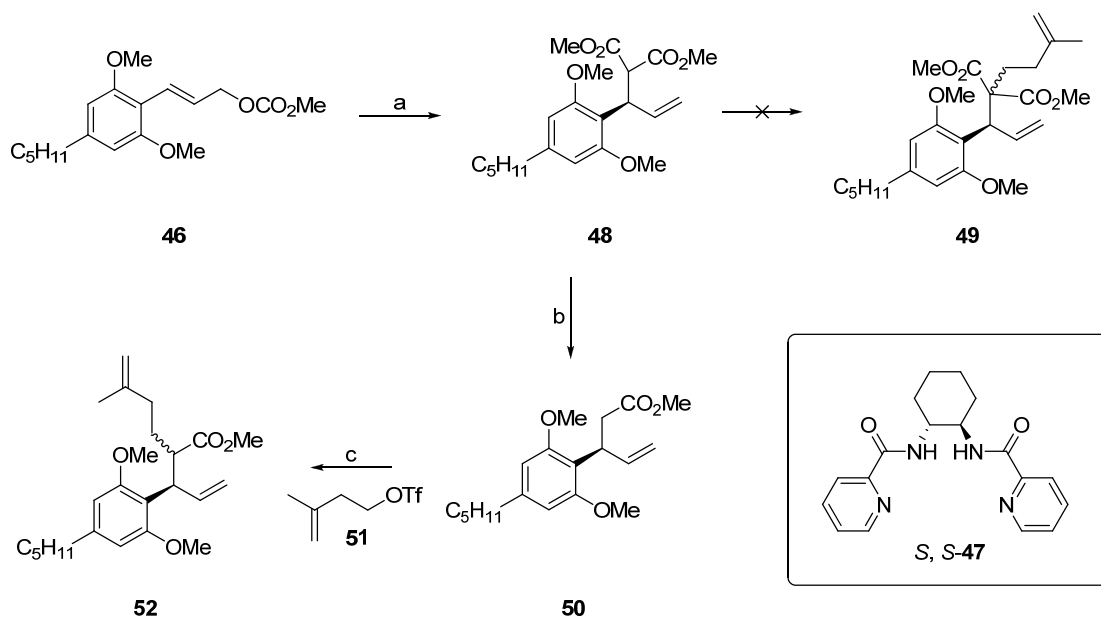
Another popular approach to cannabinoids, especially C9 substituted cannabinoids, uses a mixture of diacetates **39** and **40** derived from (-)- $\beta$ -pinene (**41**). An Eli Lilly Co. team led by Archer utilized **39** and **40** during their elegant synthesis of nabilone **6**.<sup>72</sup> Condensation of resorcinol **44** and diacetates **39** and **40** with *p*-TsOH and subsequent rearrangement/cyclization with SnCl<sub>4</sub> yielded nabilone (**6**) in 57% yield over the two steps (Scheme 1.7.2). Notably, none of the undesired abnormal cannabinoid byproduct or *cis* ring fused product was formed.



**Scheme 1.7.2** Reagents and conditions: (a) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; Me<sub>2</sub>S, -78 °C to rt; (b) isopropenyl acetate, *p*-TsOH·H<sub>2</sub>O, reflux; (c) Pb(OAc)<sub>4</sub>, PhH, reflux, 39% over two steps; (d) **44**, *p*-TsOH·H<sub>2</sub>O, CHCl<sub>3</sub>, rt, 70%; (e) SnCl<sub>4</sub>, CHCl<sub>3</sub>, rt, 84%.

$\Delta^9$ -THC is still a popular synthetic target even today, as demonstrated by the Trost group in 2007 (Scheme 1.7.3).<sup>73</sup> As Trost points out, most syntheses are either not enantioselective or derive their chirality from the chiral pool. Trost's approach

envisioned all stereochemistry resulting from a single molybdenum catalyzed asymmetric alkylation reaction. Treatment of allylic carbonate **46** with catalytic  $\text{Mo(CO)}_3\text{C}_7\text{H}_8$ , *S*, *S*-**47** and sodium dimethyl malonate resulted in **48** in 95% yield and 94% ee.



**Scheme 1.7.3** Reagents and conditions: (a) 5 mol %  $[\text{Mo(CO)}_3\text{C}_7\text{H}_8]$ , 7.5 mol % *S,S*-**47**, sodium dimethyl malonate, THF, 65 °C; 95%, 94% ee; (b) NaCl, DMSO,  $\text{H}_2\text{O}$ , 160 °C; 83%; (c) LiHMDS, THF, -40 °C, **51**; 50%.

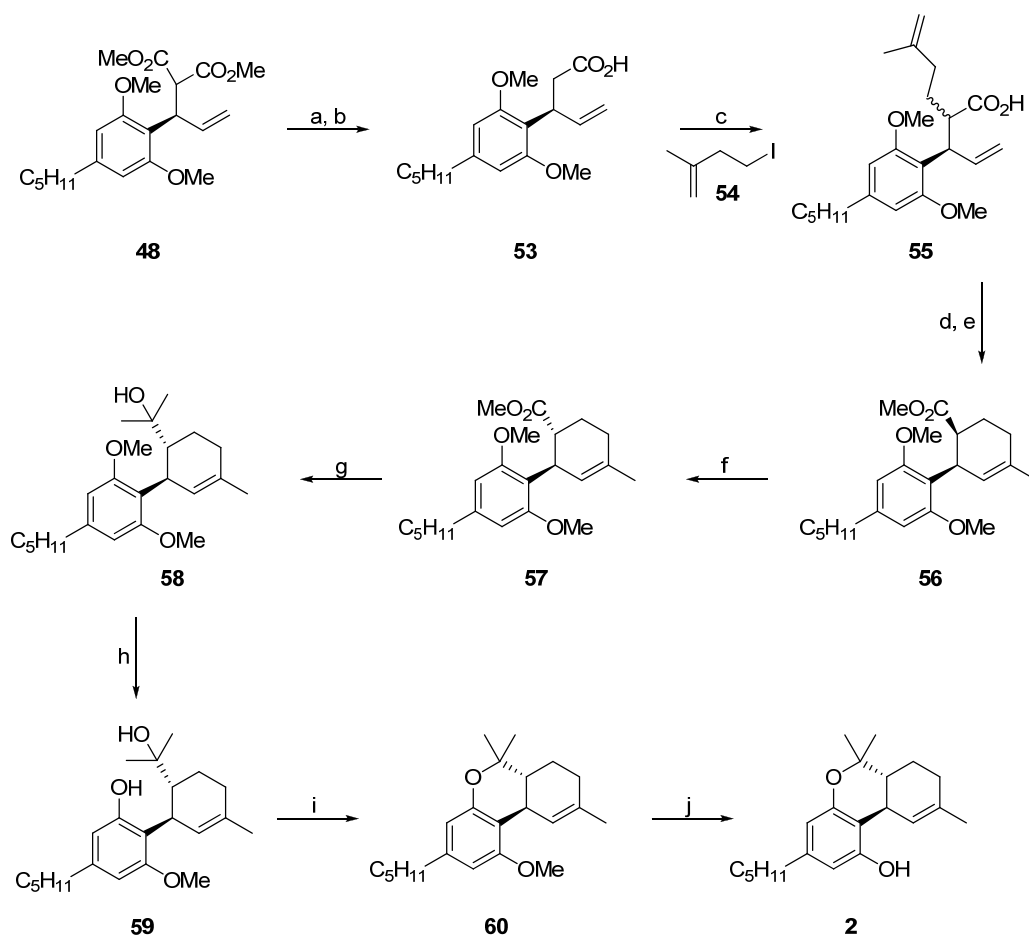
Alkylation of malonate **48** failed to yield any of the desired adduct **49** due to the steric demands of forming a quaternary carbon at the congested malonate center. To reduce the steric demands a dealkoxycarbonylation of **48** was employed followed by alkylation of **50** with triflate **51** resulting in **52** in only moderate yield (**Scheme 1.7.3**). The elimination pathway leading to isoprene was a problem due to the slower rate of alkylation at reduced temperatures. To remedy this problem the dianion from **53** was used and led to **55** in 84% yield as a 2.4:1 mixture of anti and syn isomers. The C ring

(cyclohexane) was then installed using ring closing metathesis in 81% yield.

Epimerization of the ester was realized with NaOMe in MeOH at 65 °C for three days giving **57** in 94% yield. Addition of MeLi to **57** gave the desired tertiary alcohol **58** in excellent yield. Treatment of ether **58** with BBr<sub>3</sub> or any other acidic reagents resulted in a complex mixture of products. The methyl ethers were then removed stepwise using NaSEt in DMF which is known to stop at the monodeprotection of aryl diethers.<sup>74</sup>

Treatment of phenol **59** with ZnBr<sub>2</sub> in the presence of MgSO<sub>4</sub> resulted in formation of the dihydropyran ring which was resubjected to the demethylation conditions yielding  $\Delta^9$ -THC in 61% yield and 30% yield overall from olivetol dimethyl ether (**Scheme 1.7.4**).





**Scheme 1.7.4** Reagents and conditions: (a) aqueous NaOH; HCl; (b) 160 °C, 97% over two steps; (c) LDA, THF, **54**, 0 °C to rt; 84%; (d) (MeO)<sub>2</sub>SO<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, acetone; (e) Grubbs II, CH<sub>2</sub>Cl<sub>2</sub>; 81% from **55**; (f) NaOMe, MeOH, 65 °C; 94%; (g) MeLi, Et<sub>2</sub>O, -78 °C to rt; 92%; (h) NaSEt, DMF, 140 °C; 97%; (i) ZnBr<sub>2</sub>, MgSO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (j) NaSEt, DMF, 140 °C; 61% from **59**.

## 2 Results and Discussion<sup>\*</sup>

The work described in part I of this dissertation is concerned with the synthesis and receptor binding studies of a series of  $\alpha$ -hydroxy- and  $\beta$ -hydroxyhexahydrocannabinol derivatives with a heteroadamantyl moiety at C3.

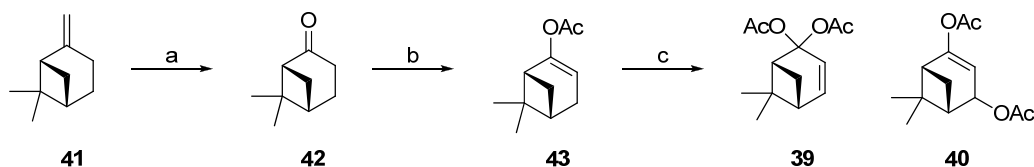
The purpose of this study was to elucidate the SAR for the C3 appendage in cannabinoids by placing heteroatoms in and around the adamantyl group. Changes in binding affinities of cannabinoids bearing heteroatoms might indicate the close proximity of polar amino acid residues within the binding pocket. Both the  $\alpha$ -hydroxy and  $\beta$ -hydroxy series were prepared as the northern aliphatic hydroxyl group is known to be an important cannabimimetic pharmacophore.

### 2.1 Stereospecific Condensation of Phloroglucinol and Nopinone Derived Diacetates

The starting material for the synthesis, diacetates **39** and **40**, were easily prepared from readily available and inexpensive (-)- $\beta$ -pinene (**41**) via ozonolysis to nopinone (**42**),<sup>75</sup> followed by enol acetate formation (**43**) and oxidation with lead (IV) acetate (**Scheme 2.1.1**). The crude diacetates were sufficiently pure (~85% pure by <sup>1</sup>H NMR) to use in the following reaction without purification.

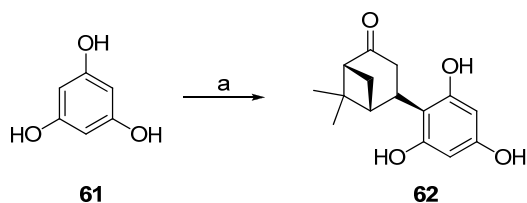
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<sup>\*</sup> Reproduced in part with permission from Dixon, D. D.; Sethumadhavan, D.; Benneche, T.; Banaag, A. R.; Tius, M. A.; Thakur, G. A.; Bowman, A.; Wood, J.; Makriyannis, A. *J. Med. Chem.* **2010**, *53*, 5656.



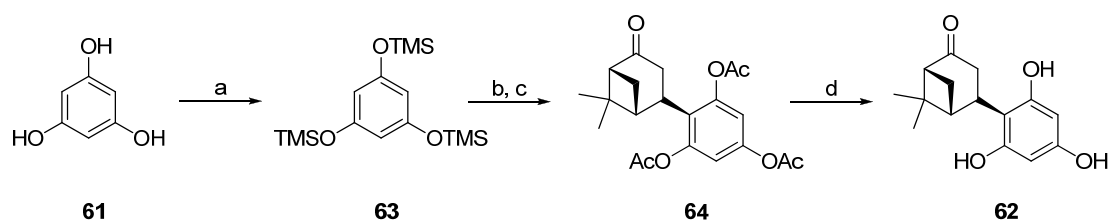
**Scheme 2.1.1** Reagents and conditions: (a)  $\text{O}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78\text{ }^\circ\text{C}$ ; thiourea,  $-78\text{ }^\circ\text{C}$  to rt; 75%; (b) isopropenyl acetate, *p*-TsOH  $\cdot$   $\text{H}_2\text{O}$ , reflux; (c)  $\text{Pb}(\text{OAc})_4$ , PhH, reflux, 72% **42**.

In order to prepare a diverse set of cannabinoids without preparing individual resorcinols we envisioned an advanced common intermediate from which all analogs could be prepared. Following an approach previously developed in our group by Dr. Le Goanvic, during the synthesis of oxazaadamantyl cannabinoids,<sup>76</sup> we chose to employ phloroglucinol (**61**) in our acid catalyzed condensation with diacetates **39** and **40**. The Eli Lilly Co. team led by Archer developed this key step during their synthesis of nabilone. Since phloroglucinol is sparingly soluble in  $\text{CH}_2\text{Cl}_2$  a mixed solvent system of 4/1  $\text{CH}_2\text{Cl}_2$ /acetone was used to overcome this problem. Bicyclic intermediate **62** was obtained in a moderate yield of 40% which can be attributed to the high reactivity of **61** which can lead to condensation with a second molecule of **39** or **40** (Scheme 2.1.2).



**Scheme 2.1.2** Reagents and conditions: (a) *p*-TsOH  $\cdot$   $\text{H}_2\text{O}$ , **39** and **40**, 4/1  $\text{CH}_2\text{Cl}_2$ /acetone, rt; 40%.

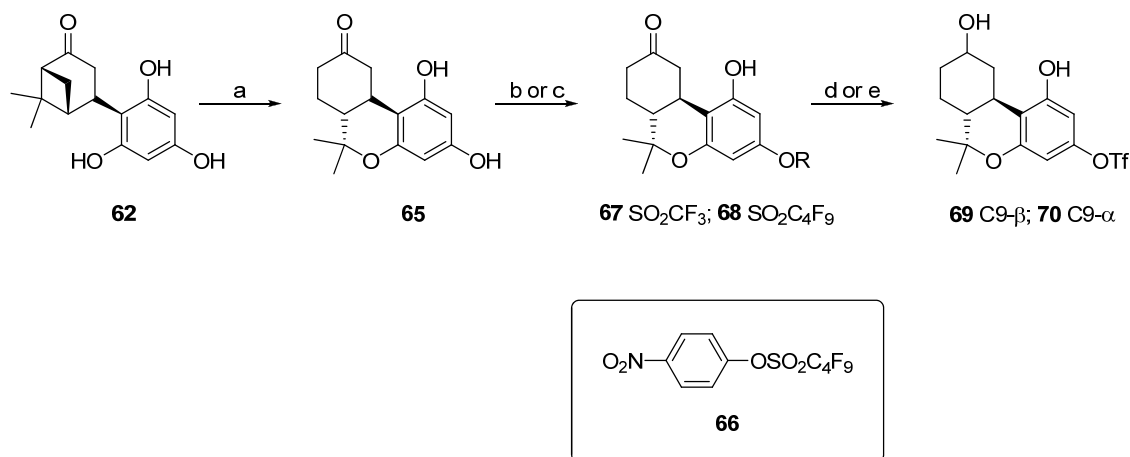
It should be noted that through the years of cannabinoid research conducted in the Tius lab, chloroform was found to be the optimal solvent for the condensation reaction and any deviation from this solvent results in decreased yields. After screening various reaction conditions we were eventually able to devise a simple modification to overcome the solubility issues associated with phloroglucinol. Exposure of phloroglucinol to TMSCl and TEA in CH<sub>2</sub>Cl<sub>2</sub> led to hydrolytically sensitive persilylated phloroglucinol **63** which was not purified and used immediately in the condensation with **39** and **40**. Masking the phenolic hydroxyl groups as the TMS ethers drastically increased solubility in CHCl<sub>3</sub> and allowed us to run the reaction in a 4/1 mixture of CHCl<sub>3</sub>/acetone with a slight excess of *p*-TsOH·H<sub>2</sub>O. This led to a much cleaner reaction and formed **62** in 70% yield with negligible bis-condensation byproduct. The separation of bicyclic adduct **62** and excess phloroglucinol proved to be difficult so the crude reaction mixture was treated with Ac<sub>2</sub>O, pyridine and catalytic DMAP in CH<sub>2</sub>Cl<sub>2</sub> yielding triacetate **64**. Separation of **64** and acetylated **61** was straightforward and pure **62** could be isolated after hydrolytic cleavage of the acetates with methanolic KOH in 68% yield over the three steps (**Scheme 2.1.3**).



**Scheme 2.1.3** Reagents and conditions: (a) TMSCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt; (b) *p*-TsOH·H<sub>2</sub>O, 4/1 CHCl<sub>3</sub>/acetone, 0 °C to rt; (c) Ac<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, DMAP (cat.), pyridine, 0 °C to rt; (d) KOH, MeOH, 0 °C; 68% overall from **39** and **40**.

## 2.2 Synthesis of Amide Analogs

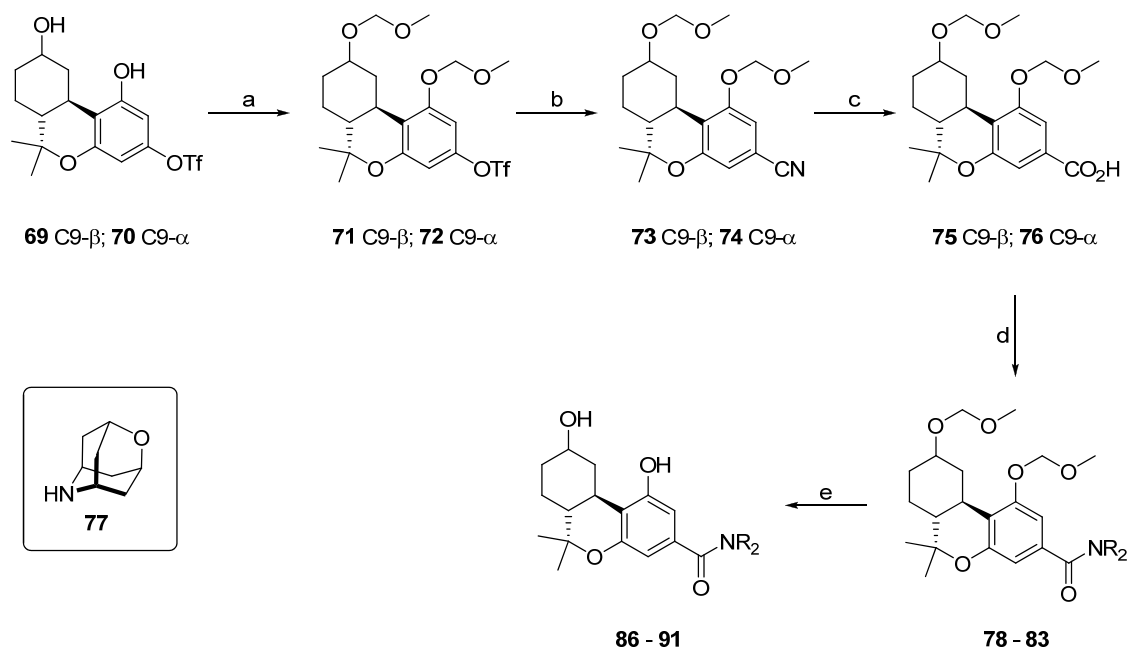
In Le Goanvic's synthesis of the oxazaadamantanes,<sup>76</sup> SnCl<sub>4</sub> was used as the Lewis acid to promote the rearrangement and cyclization to give **65**. On small scale this proved to be practical but on scale up, the formation of emulsions and tin salts resulted in irreproducible product yields. After screening other Lewis acids, TMSOTf proved to be a much better choice than SnCl<sub>4</sub> in terms of ease of workup as well as the yield (>95% vs. 84%) resulting in **65** which could be used without further purification. Another improvement was the use of *N*-phenyltriflimide<sup>77</sup> and TEA in CH<sub>2</sub>Cl<sub>2</sub> over the nonaflyl transfer reagent **66**<sup>78</sup> and CsF in DMF in the selective sulfonylation of **65** (51% vs. 68%). Triflate **67** could be obtained in 68% yield in a single operation or in 57% from **62** requiring only one purification step. Since both diastereomers of the C9 alcohol were going to be investigated, ketone **68** was reduced with NaBH<sub>4</sub> in 97% yield as a 95/5 mixture of C9-β (equatorial) alcohol **69** to C9-α (axial) alcohol diastereomer **70**. Alcohol **70** could be obtained as the sole diastereomer when ketone **67** was treated with L- or K-Selectride at -78 °C (Scheme 2.2.1).



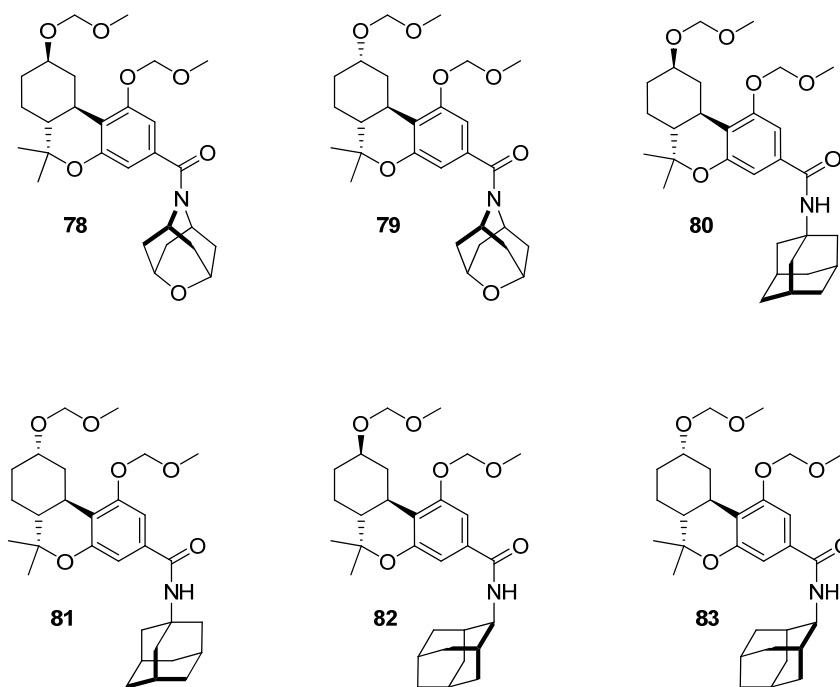
**Scheme 2.2.1** Reagents and conditions: (a) TMSOTf, MeNO<sub>2</sub>, 0 °C; (b) PhNTf<sub>2</sub>, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt; 57% from **62**; (c) CsF, DMF, **66**, rt; 57%; (d) NaBH<sub>4</sub>, MeOH, 0 °C; 97% **69** + **70**, ca. 95/5; (e) L-Selectride, THF, -78 °C; rt, 90%.

The aliphatic and phenolic hydroxy groups of **69** and **70** were simultaneously protected as the methoxymethyl ether, resulting in **71** and **72** in 93% and 94% respectively.

Exposure of triflate **71** and **72** to catalytic Pd(PPh<sub>3</sub>)<sub>4</sub> and Zn(CN)<sub>2</sub> in DMF at 60 °C led to nitriles **73** and **74**, respectively, in excellent yield. The reproducibility of this reaction proved to be problematic, and the addition of 10 wt. % PMHS<sup>79</sup> as an oxygen scavenger was required to obtain the nitriles in consistent yields of >95%. Hydrolysis of nitriles **73** and **74** with LiOH in aqueous methanol gave acids **75** and **76** in 91% yield for each isomer. Exposure of acids **75** and **76** to EDCI and DMAP in CH<sub>2</sub>Cl<sub>2</sub> to oxazaadamantane (**77**), 1-adamantylamine and 2-adamantylamine led to amides **78** (91%), **79** (88%), **80** (90%), **81** (91%), **82** (90%) and **83** (91%) (**Scheme 2.2.2**). All protected amide derivatives are shown in **Figure 2.2.1**.



**Scheme 2.2.2** Reagents and conditions: (a)  $\text{MeOCH}_2\text{Cl}$ ,  $(i\text{-Pr})_2\text{NEt}$ ,  $\text{CH}_2\text{Cl}_2$ , 0 °C to rt; **71**, 93%; **72**, 94%; (b)  $\text{Zn}(\text{CN})_2$ ,  $\text{Pd}(\text{PPh}_3)_4$  (cat.), 10 wt % PMHS, DMF, 60 °C; **73**, 96%; **74**, 97%; (c)  $\text{LiOH}$ , 4/1  $\text{MeOH}/\text{H}_2\text{O}$ , 70 °C; **75**, 91%; **76**, 91%; (d) **77**, 1-adamantylamine or 2-adamantylamine, EDCI, DMAP,  $\text{CH}_2\text{Cl}_2$ , rt; from **75**: **78**, 91%; **80**, 90%; **82**, 90%; from **76**: **79**, 88%; **81**, 91%; **83**, 91%; (e)  $n\text{-BuSH}$ ,  $\text{ZnBr}_2$ ,  $\text{CH}_2\text{Cl}_2$ , 45 °C; **86**, 77%; **87**, 89%; **88**, 89%; **89**, 92%; **90**, 91%; **91**, 90%.

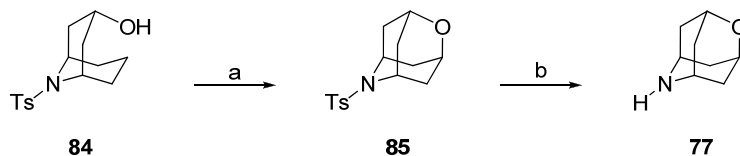


**Figure 2.2.1** Protected amide analogs.

It should also be noted that the synthesis of oxazaadamantane **77** was improved. Le Goanvic reported 50% yield for the photochemical oxidative closure of alcohol **84** to the pyran ring<sup>76, 80</sup> and 48% yield for the reductive cleavage of the tosylate **85**. The yield for the oxidative ring closure can be improved drastically (75% vs. 50%) when finely powdered alcohol **84** and  $\text{PhI}(\text{OAc})_2$  are used as well as focusing the light source as close to the reaction flask as possible with aluminum foil surrounding the flask to ensure maximum exposure to the light source. Also, the yield for the reductive cleavage of the tosylate is greatly improved by limiting the amount of acid introduced to quench the reaction. Introducing just enough saturated  $\text{NH}_4\text{Cl}$  to dissipate the dark green color of the sodium naphthalide ensures minimal product loss. A simple acid-base workup is then

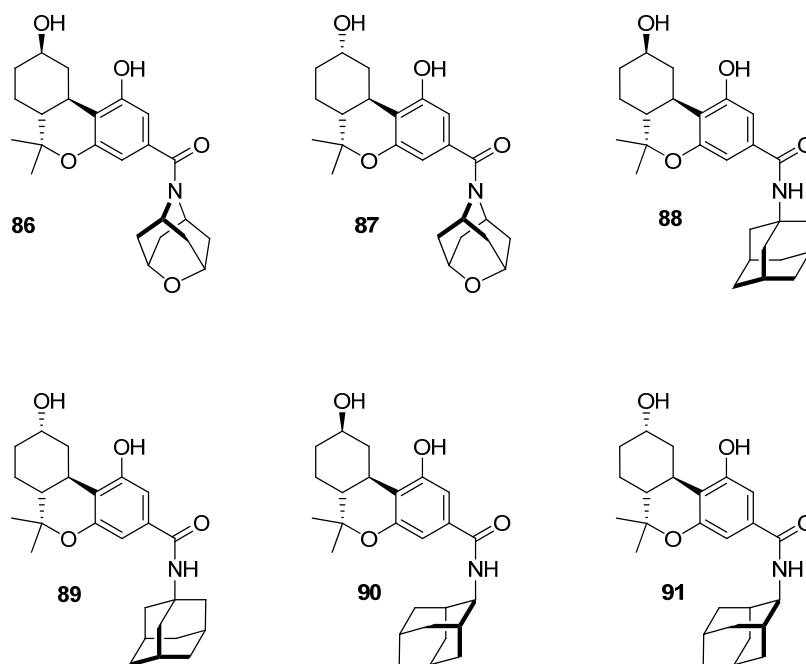


used to remove excess naphthalene and to recover the pure oxazaadamantane **77** in 85% yield (**Scheme 2.2.3**).



**Scheme 2.2.3** Reagents and conditions: (a)  $\text{PhI}(\text{OAc})_2$ ,  $\text{I}_2$ ,  $h\nu$ ,  $\text{C}_6\text{H}_{12}$ ,  $50\text{ }^\circ\text{C}$ ; 75%; (b) Na, naphthalene, DME,  $-50\text{ }^\circ\text{C}$ ; 85%.

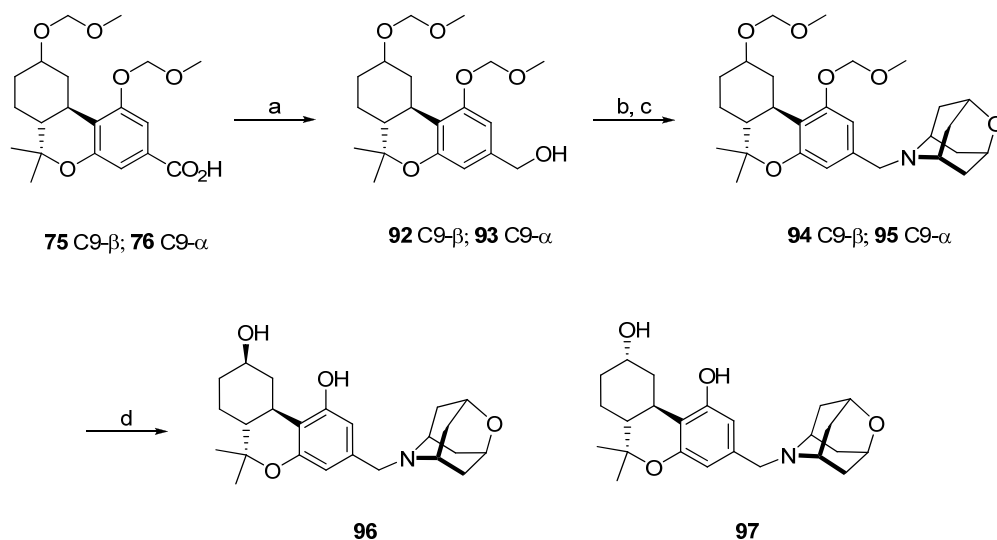
Removal of the methoxymethyl ether protecting groups proved to be more challenging than expected. Conventional deprotection methods (HCl, PPTS) led to diol products in less than 50% yield and long reaction times. Deprotection could be realized with  $\text{TMSBr}$ <sup>81</sup> in  $\text{CH}_2\text{Cl}_2$  at  $-40\text{ }^\circ\text{C}$  but the optimal conditions were treatment with  $\text{ZnBr}_2$  and  $n\text{-BuSH}$  in  $\text{CH}_2\text{Cl}_2$  at  $45\text{ }^\circ\text{C}$  as described by Rawal.<sup>82</sup> All amides prepared are shown in **Figure 2.2.2**.



**Figure 2.2.2** Amide analogs.

### 2.3 Synthesis of Amine Analogs

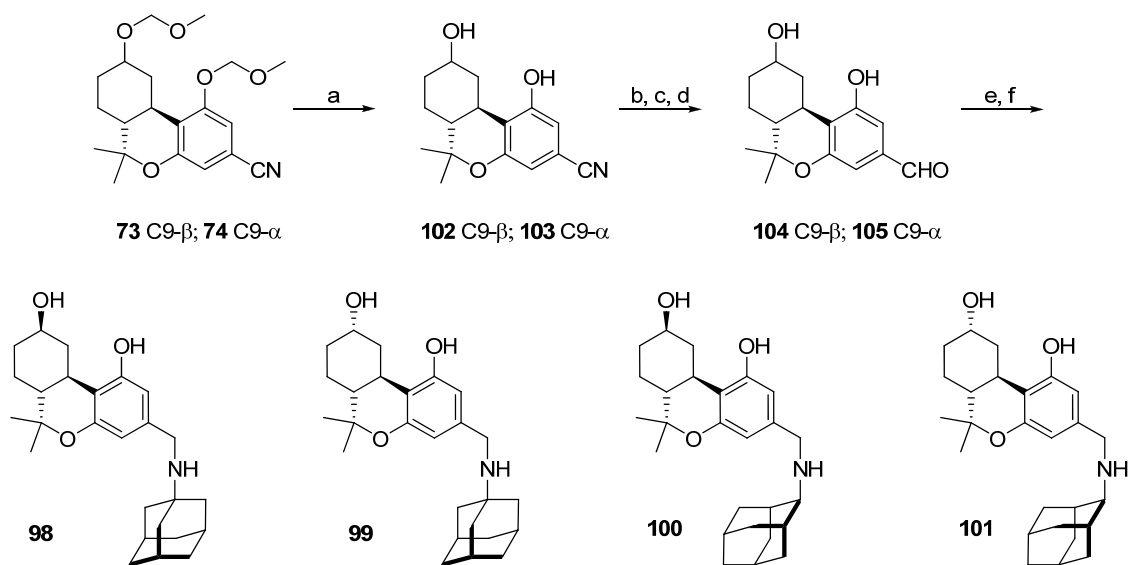
The next class of compounds to be synthesized was the amino analogs which incorporated a methylene spacer between **77** and the tricyclic cannabinoid nucleus. Our initial approach involved reduction of the protected amides (**78** and **79**) with LAH or Singaram's LAB (lithium amino borane) reagent<sup>83</sup> followed by removal of the protecting groups, but this was unsuccessful. Since reduction of the amide proved to be problematic we envisioned displacement of a benzylic halide with oxazaadamantane **77**.



**Scheme 2.3.1** Reagents and conditions: (a)  $\text{BH}_3 \cdot \text{THF}$ , THF,  $0^\circ\text{C}$ ;  $0^\circ\text{C}$  to rt; **75**, 88%; **76**, 88%; (b)  $\text{MsCl}$ ,  $\text{Et}_3\text{N}$ , THF,  $0^\circ\text{C}$  to rt;  $\text{LiBr}$ , THF, rt; (c) **77**, DMF,  $\text{K}_2\text{CO}_3$ , rt; **94**, 75%; **95**, 72%; (d)  $n\text{-BuSH}$ ,  $\text{ZnBr}_2$ ,  $\text{CH}_2\text{Cl}_2$ ,  $45^\circ\text{C}$ ; **96**, 81%; **97**, 73%.

Reduction of carboxylic acids **75** and **76** with  $\text{BH}_3 \cdot \text{THF}$  or  $\text{BH}_3 \cdot \text{SMe}_2$  complex led to benzylic alcohol diastereomers **92** and **93**, each in 88% yield (**Scheme 2.3.1**). Treatment of the diastereomeric alcohols with  $\text{MsCl}$  and immediate displacement by bromide gave the diastereomeric benzyl bromides which were used without purification. Exposure of the diastereomeric bromides to a slight excess of **77** in the presence of  $\text{K}_2\text{CO}_3$  in DMF led to oxazaadamantylamines **94** and **95** in 75% and 72% yield, respectively. All attempts to remove the methoxymethyl ether protecting groups with  $\text{TMSBr}$  as reported by Le Goanvic led to very low yields. This is quite likely due to the buffering effect of the basic nitrogen atom. The conditions developed by Rawal and co-workers proved to be optimal for removing the methoxymethyl ethers, yielding amines **96** and **97** in 81% yield and 73% yield, respectively.

A slightly different strategy was followed for the synthesis of the secondary adamantylamines (**98 - 101**) (Scheme 2.3.2). With the increased difficulty of removing the methoxymethyl ethers from **94** and **95** we wanted to devise a strategy that did not involve the removal of the methoxymethyl ether protecting groups in the presence of a secondary amine. Removal of the methoxymethyl ethers in the presence of the aldehyde took place in very low yield, making the protecting group exchange necessary. Nitriles **73** and **74** were treated with ZnBr<sub>2</sub> and *n*-BuSH at room temperature yielding diastereomeric alcohols **102** and **103**. The hydroxyl groups were then temporarily masked as triethylsilyl ethers followed by reduction of the nitrile to the aldehyde and fluorodesilylation to produce **104** and **105**, each in 61% yield over the three steps. Treatment of aldehydes **104** and **105** with 1-adamantylamine or 2-adamantylamine under Dean-Stark conditions formed the sensitive imine which underwent catalytic hydrogenation with 10% Pd/C in MeOH under an atmosphere of hydrogen resulting in the clean formation of adamantylamines **98 – 101**.

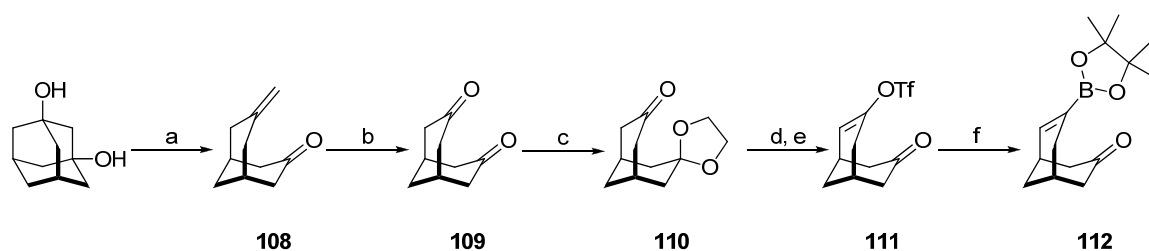


**Scheme 2.3.2** Reagents and conditions: (a) *n*-BuSH, ZnBr<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt; **73**, 90%, **74**, 76%; (b) Et<sub>3</sub>SiCl, (*i*-Pr)<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt; (c) DIBAL, CH<sub>2</sub>Cl<sub>2</sub>, PhMe, -78 °C; (d) TBAF, THF, rt; **104**, 61% from **102**; **105**, 61% from **103**; (e) PhH, 1- or 2-adamantylamine, 4 Å MS, reflux, Dean-Stark; (f) Pd/C, H<sub>2</sub>, MeOH, rt; **98**, 81% from **104**; **99**, 78% from **105**; **100**, 60% from **104**; **101**, 84% from **105**.

## 2.4 Synthesis of Oxaadamantane Analogs

The synthesis of oxaadamantanes **106** and **107** proved to be quite challenging (**Scheme 2.4.2**). Initially we had planned to utilize an approach that had served us well in the past involving trapping of a benzyne intermediate with a carbon nucleophile. Ultimately, we were unable to define successful reaction conditions and were forced to abandon this approach in favor of a cross coupling process. Suzuki-Miyaura cross coupling of triflate **71** or **72** with an appropriate vinyl boronate would allow us to install functionality that would be transformed into the oxaadamantane system. Treatment of commercially available 1,3-adamantanediol with benzenesulfonyl chloride<sup>84</sup> in a mixture of pyridine

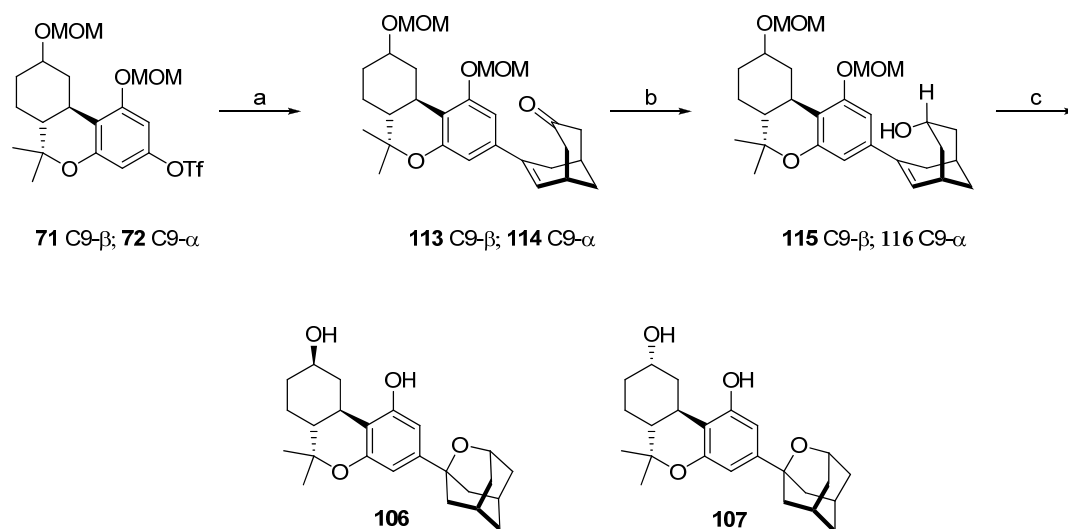
and benzene at 70 °C led to Grob fragmentation product **108**. Ozonolysis of crude alkene **108** gave diketone **109** in 66% yield over the two steps. It should be noted that the use of CH<sub>2</sub>Cl<sub>2</sub> rather than CH<sub>2</sub>Cl<sub>2</sub>/MeOH resulted in consistently higher yields due to the formation of a methoxy hemiketal in the mixed solvent system. The hemiketal byproduct can be hydrolyzed to release diketone **109** with concentrated acid in aqueous THF. Selective protection of one of the two carbonyl groups as the ethylene ketal formed **110** in 94% yield. Reaction times must be kept short in order to prevent the formation of the bis-ketal product. Treatment of ketone **110** with LDA in THF at -78 °C with PhNTf<sub>2</sub> followed by acid catalyzed exchange of the ketal led to triflate **111** in 82% yield for the two steps. Suzuki coupling of **111** with *bis*-pinacolato diborane led to vinyl boronate **112** in good yield (Scheme 2.4.1).<sup>85, 86</sup>



**Scheme 2.4.1** Reagents and conditions: (a) PhSO<sub>2</sub>Cl, PhH, pyridine, 70 °C; (b) O<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C; Me<sub>2</sub>S; 66% for two steps; (c) HO(CH<sub>2</sub>)<sub>2</sub>OH, PhH, TsOH (cat.), reflux, Dean-Stark; 94%; (d) LDA, THF, -78 °C; PhNTf<sub>2</sub>, THF, -78 °C to 0 °C; (e) acetone, TsOH (cat.), rt; 82% from **110**; (f) PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub>, PPh<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, 1,4-dioxane, PinB-BPin, 70 °C; 73%.

Tricyclic intermediates **71** and **72** were then coupled with vinyl boronate **112**. Treatment of a slight excess of **112** with PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub> and aryl triflates **71** and **72** in a 4/1 mixture of DMF/EtOH at 70 °C led to coupled products **113** and **114** in 87% and

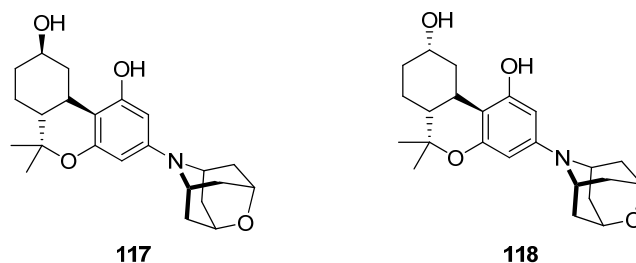
67% yield, respectively. Because **112** is racemic whereas **71** and **72** are homochiral, products **113** and **114** are formed in diastereomeric mixtures. For the sake of simplicity, only one diastereomeric structure is shown in **Scheme 2.4.1**. Treatment of ketones **113** and **114** with NaBH<sub>4</sub> led exclusively to the *endo* alcohols **115** and **116**. Immediate purification was required to obtain high yields due to the premature cyclization of the crude material that occurs upon standing. Exposure of **115** and **116** to ZnBr<sub>2</sub> and *n*-BuSH at room temperature removed the methoxymethyl ether protecting groups and induced cyclization forming **106** and **107** in 95% yield and 79% yield, respectively (**Scheme 2.4.2**).



**Scheme 2.4.2** Reagents and conditions: (a) **112**, PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub>, DMF/EtOH (4/1), 70 °C; **113**, 87%; **114**, 67%; (b) NaBH<sub>4</sub>, MeOH, 0 °C; **115**, 90%; **116**, 82%; (c) *n*-BuSH, ZnBr<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt; **106**, 95%; **107**, 79%.

### 3 Receptor Binding Studies and Molecular Modeling

Receptor binding studies and molecular modeling of all final compounds were conducted at Northeastern University, Center for Drug Discovery under the direction of Professor Alexandros Makriyannis. Competitive binding assays with the radioligand [ $^3\text{H}$ ]-CP-55,940 (**3**) were carried out using rat brain or membranes from HEK293 cells to assess the affinities for the CB1 and CB2 receptor binding sites, respectively, following previously described procedures. A series of experiments were conducted for each compound at varying concentrations and the results of which will be discussed in detail in this chapter. The two oxazaadamantyl cannabinoids, **117** and **118**, prepared by Dr. David Le Goanvic will also be discussed in this section for completeness sake (**Figure 3.1**).



**Figure 3.1** Oxazaadamantyl cannabinoids prepared by Dr. David Le Goanvic.

Earlier work from the Makriyannis laboratory<sup>87</sup> showed that the 1-adamantyl cannabinoid AM-411 exhibited preferential affinity for CB1 while the 2-adamantyl analog AM-744 had higher affinity for CB2. To probe the stereoelectronic properties of the adamantyl group and to explore potential opportunities to improve the polar properties of the adamantyl cannabinoid ligands we introduced heteroatoms throughout the adamantyl



group. The small library of compounds that were prepared can be divided into three groups. The first group includes the analogs with the 2-oxaadamantyl and 2,6-oxazaadamantyl substituent directly attached to the C3 position of the tricyclic nucleus (**106**, **107**, **117** and **118**). The second group has heteroatoms incorporated into the carbocyclic 1- or 2-adamantyl residue appended at C3 through a carbonyl (**88-91**) or methylene spacer (**98-101**). Finally, the third group has the 2,6-oxazaadamantyl residue attached to C3 through a carbonyl (**86** and **87**) or methylene spacer (**96** and **97**). Binding affinities for all compounds for CB1 and CB2 cannabinoid receptors are shown in **Table 3.1**.

**Table 3.1** Affinities ( $K_i$ ) for CB1 and CB2 cannabinoid receptors.

Compound	$K_i$ ( $\mu\text{M}$ ) <sup>a</sup>		
	rCB1	mCB2	hCB2
<b>1</b> <sup>46</sup>	0.0068	0.052	N.A.
<b>Group 1</b>			
<b>106</b>	0.023	0.018	0.019
<b>107</b>	0.55	0.54	1.3
<b>117</b>	1.8	1.2	1.8
<b>118</b>	22.4	17	14.9
<b>Group 2</b>			
<b>88</b>	80	0.5	8.7
<b>89</b>	375	7.5	35
<b>90</b>	15	1.2	2.7
<b>91</b>	100	3.7	15
<b>98</b>	150	0.5	10
<b>99</b>	100	5	25
<b>100</b>	150	6.2	20
<b>101</b>	No binding	7.5	25

**Table 3.1** Continued.

<b>Group 3</b>			
<b>86</b>	No binding	2.5	20
<b>87</b>	No binding	8.6	25
<b>96</b>	10	8.7	15
<b>97</b>	125	7.5	5

<sup>a</sup> K<sub>i</sub> values for compounds **117**, **118**, **106** and **107** were obtained from one experiment (8 point) run in triplicate. K<sub>i</sub> values for compounds **88 - 91** and **98 - 101** which were all in the micromolar range were derived from a single experiment (2 points) run in triplicate.

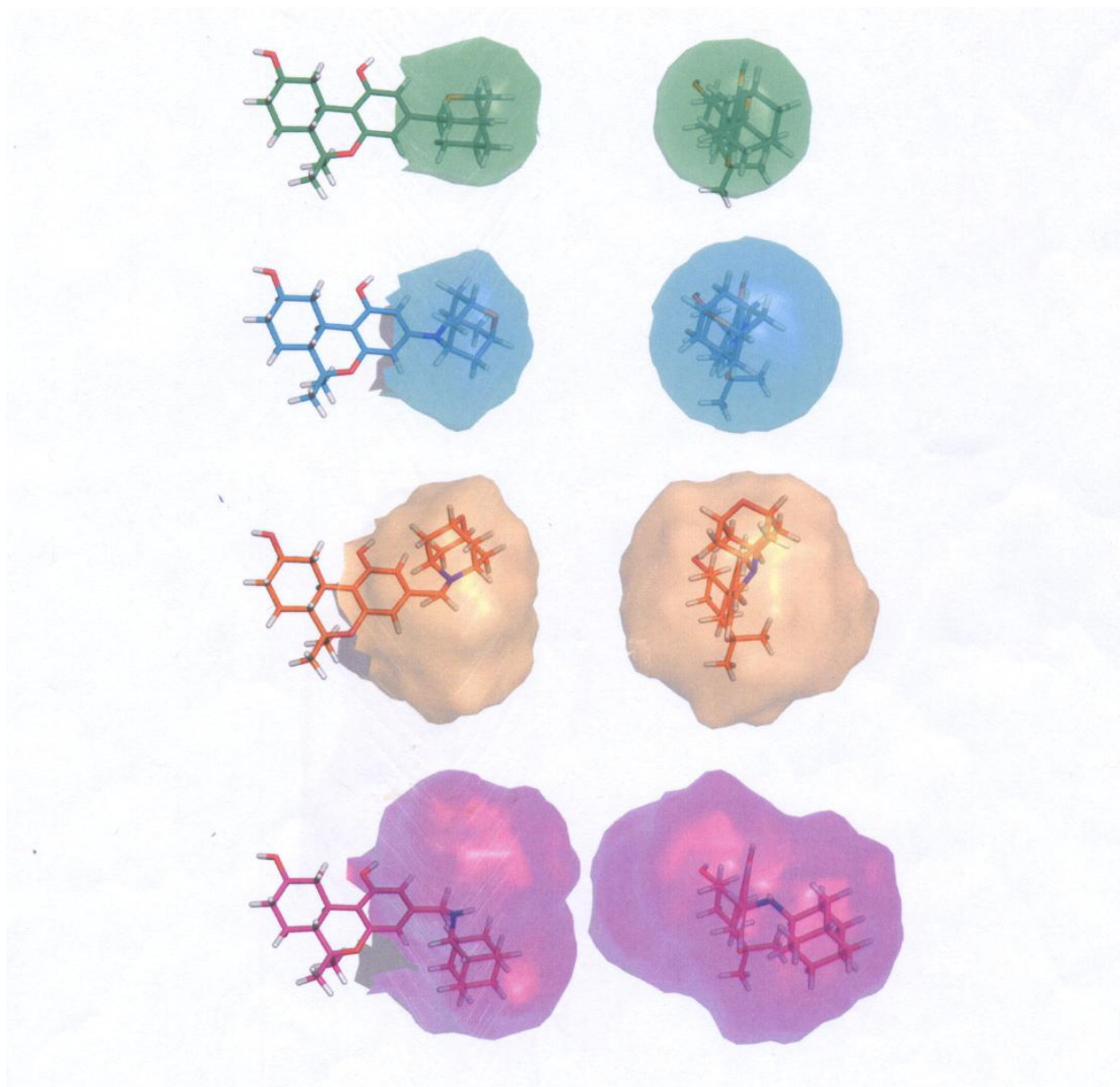
The oxazaadamantyl cannabinoids displayed reduced affinities for the CB1 and CB2 receptors when compared to their carbocyclic counterparts, AM-411 and AM-744. All analogs containing the C9  $\beta$ -hydroxy showed stronger affinities to both receptors when compared to the C9  $\alpha$ -hydroxy analogs which is congruent with earlier data (For example: **106** and **107**). All compounds belonging to the second group (**88 – 91** and **98 - 101**) had low affinities for both receptors but showed considerable selectivity for CB2 over CB1. This suggests that the CB2 receptors in humans and mice are capable of accommodating larger side chain substituents when compared to CB1. It also suggests that the mouse CB2 receptor is able to accommodate larger groups compared to the human CB2 receptor.

The third group displayed lower affinities than the carbocyclic counterparts while maintaining selectivity for CB2 (see **Table 3.1**). Again, the mouse CB2 receptor showed slightly stronger affinities than the human CB2 receptor.

The analogs of the first group are the most structurally compact and similar to the potent cannabinoid AM-411. We were pleased to find that **106** showed favorable affinities for both receptors. Surprisingly, **106** showed a different pharmacological profile than AM-411. Oxaadamantane **106** showed modest selectivity for CB2 while AM-411 is CB1 selective. This result could be due to the presence of the oxygen atom in the adamantyl group which results in increased polarity (clogP) compared to AM-411 and may suggest that a hydrogen bond is formed in the active site of the binding pocket of the CB2 receptor.

To explain the observed differences of the three groups, molecular modeling was used. Since the only pharmacophoric variable was the substituent at C3, the focus was on the stereoelectronic and conformational properties as well as the available conformational space for the C3 substituents. Force field methods were used and retained all conformers within 6 kcal/mol of the global minimum.

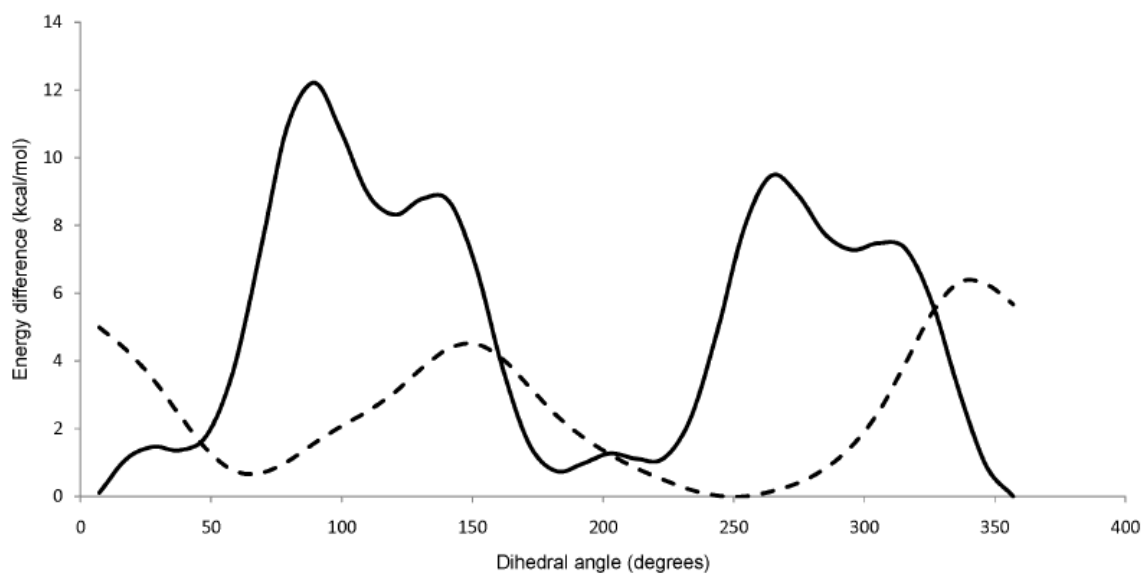
The second and third groups cover a significantly larger volume which can be attributed to the low affinity of these compounds. The large desolvation penalties due to the polar nature of the linkers as well as the bulkiness of these substituents do not allow for optimal interaction with the pharmacophoric site in the cannabinoid receptors. A representative example from each group is shown in **Figure 3.2** with accessible conformers within 6 kcal/mol of the global minimum energy and analogs are shown superimposed at their aromatic rings.



**Figure 3.2** Pharmacophoric space for group 1 [**106** (green), **117** (cyan)], group 2 [**100** (magenta)] and group 3 [**97** (orange)].

Meanwhile, the low affinities for oxazaadamantyl cannabinoids **117** and **118** can not be explained using the pharmacophoric space argument since there is no striking difference

in the accessible conformational volumes compared to the oxaadamantyl analogs. In order to explain the differences in binding affinity between the oxazaadamantyl and oxaadamantyl analogs, the energy barrier for rotation around the C3-C1' bond were investigated. To explore these permissible rotations of the C3 substituents a conformational search was performed using the OPLS force field<sup>88, 89</sup> with the tricyclic moiety held fixed with minimization on the geometric parameters being performed. All calculations were performed on Macromodel<sup>90</sup> and conformers with greater than 0.5 Å root mean square deviation within 6 kcal/mol of the global minimum were retained. Also, entropic factors of **106** and **117** were of interest and calculations were performed at the B3LYP/6-31G\*\* level. A plot of the energy barriers of rotation for **106** and **117** are shown in **Figure 3.3**. The calculations revealed that the oxaadamantyl analogs have a rotational barrier of approximately 6.3 kcal/mol while the oxazaadamantyl analogs have a significantly higher barrier of approximately 12.3 kcal/mol. It can be argued that while both analogs in question occupy similar conformational spaces, entropic advantages associated with the more facile rotation of the oxaadamantyl moiety may improve ligand binding affinity. It is also possible that the nitrogen and oxygen atoms of the 2, 6-oxazaaadamantane moiety undergo unfavorable interactions within its allowable pharmacophoric space.



**Figure 3.3** Energy barriers for rotation of **106** (dashed) and **117** (solid) about the C3-C1' bond.

## 4 Conclusion

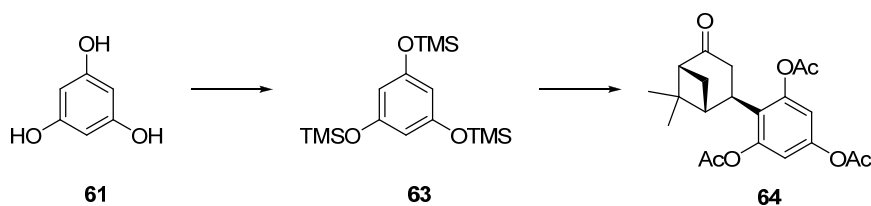
In conclusion, the design and execution of new synthetic approaches to several C3 substituted heteroadamantyl cannabinoids and analogs thereof have been described. The key steps in the synthetic scheme are the condensation of persilylated phloroglucinol with nopinone derived diacetates, TMSOTf catalyzed rearrangement and cyclization to form the dihydropyran, selective triflation of the hydroxyl at C3, stereoselective reduction at C9, palladium catalyzed cyanation, and Suzuki-Miyaura cross coupling between a vinyl boronate and aryl triflate. All analogs showed at least micromolar affinity for the receptors and selectivity for CB2 over CB1. The C9  $\beta$ -hydroxy 2-oxaadamantyl analog had the highest affinity for CB2 ( $K_i = 18.5$  nM) and showed a slight preference for CB2 over CB1 and will be tested in a rat behavioral model. Molecular modeling of the analogs showed that the presence of a carbonyl or methylene linker at C1' drastically increases the pharmacophoric space resulting in decreased binding affinity. This work also confirmed that the C9  $\beta$ -hydroxy analogs have higher affinities compared to the C9  $\alpha$ -hydroxy analogs, that space for the adamantyl pharmacophore is most restricted at CB1 and that there appears to be a species difference with the mouse CB2 receptor being more accommodating for steric bulk at C3 than human CB2. Functionalization of the Suzuki-Miyaura product can also be envisioned as an intermediate to form novel oxaadamantane derivatives with reactive functional groups present to act as covalent probes which are currently in progress.



## 5 Experimental Section

### General:

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Varian Mercury Plus 300 ( $^1\text{H}$  300 MHz,  $^{13}\text{C}$  75 MHz) or a Varian Unity INOVA 500 ( $^1\text{H}$  500 MHz,  $^{13}\text{C}$  126 MHz) in either deuteriochloroform ( $\text{CDCl}_3$ ;  $^1\text{H}$  7.26 ppm,  $^{13}\text{C}$  77.0 ppm), deuterobenzene ( $\text{C}_6\text{D}_6$ ;  $^1\text{H}$  7.15 ppm,  $^{13}\text{C}$  128.0 ppm) or deuteromethanol ( $\text{CD}_3\text{OD}$ ;  $^1\text{H}$  3.31 and 4.90 ppm,  $^{13}\text{C}$  49.0 ppm). Chemical shifts are given in  $\delta$ , with multiplicities given as s (singlet), br (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or a combination thereof and  $J$  (coupling constants) given in hertz (Hz). IR spectra were recorded on a Nicolet 380 FT-IR using a NaCl plate. Mass spectral data was collected on either an Agilent 1100 Series LC-MS TOF ( $\text{ESI}^+$  or  $\text{APCI}^+$  source) or VG-70SE ( $\text{EI}^+$  source). Optical rotation data was collected on a JASCO DIP-370 digital polarimeter. Melting points were collected on a Mel-Temp II melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using Sigma-Aldrich silica-gel, general-purpose TLC plates with UV indicator ( $\text{F}_{254}$ ). Flash chromatography was performed using Silicycle SiliaFlash F60 silica gel (230-400 mesh). All solvents used were purified using a solvent purification system. The purity of assayed compounds were of at least 95% and were verified using high performance liquid chromatography on an Agilent 1200 Series or a Beckman Coulter System Gold HPLC equipped with Daicel Chiralpak AD-H (4.6 x 250 mm), Luna C8(2) (1 x 250 mm) or Chiralcel OD-H (4.6 x 250 mm) column.



To a suspension of phloroglucinol **61** (5.50 g, 43.7 mmol) in 300 mL of  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  was added TEA (24.3 mL, 174.6 mmol) followed by  $\text{TMSCl}$  (22.3 mL, 174.6 mmol). After 20 min the cooling bath was removed and the mixture was allowed to stir at room temperature for an additional 2 h. The salts were removed *via* filtration and the filtrate was washed with ice cold water (3x), dried over  $\text{Na}_2\text{SO}_4$  and concentrated affording persilylated phloroglucinol **63**. Crude **63** was then dissolved in 440 mL of a 4:1 mixture of  $\text{CHCl}_3$ :acetone and cooled to  $0^\circ\text{C}$ . In a separate flask diacetates **39** and **40** (4.42 g, 18.6 mmol; 5.2 g of 85% pure diacetates **39** and **40** were used) were dissolved in 150 mL of 4:1  $\text{CHCl}_3$ :acetone along with  $\text{TsOH}\cdot\text{H}_2\text{O}$  (4.57 g, 24.0 mmol). The  $\text{TsOH}\cdot\text{H}_2\text{O}$  and diacetates mixture was then added dropwise to persilylated phloroglucinol **63** at a rate of approximately one drop/s *via* an addition funnel. The reaction mixture was then slowly warmed to room temperature. Once the diacetates were shown to be consumed (monitored by TLC) the reaction was quenched with saturated  $\text{NaHCO}_3$  and stirred for 45 min. The organic layer was separated and dried over  $\text{MgSO}_4$ , while the aqueous layer was back-extracted with  $\text{EtOAc}$  (6x) and dried over  $\text{MgSO}_4$ . To the crude condensation product **62** and DMAP (100 mg, 0.82 mmol) in 200 mL of  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  was added pyridine (13.0 mL, 160.0 mmol) followed by  $\text{Ac}_2\text{O}$  (15.1 mL, 160.0 mmol). The mixture was stirred for 12 h before being quenched with ice cold water, washed sequentially with

1 M HCl, brine then dried over MgSO<sub>4</sub>. The crude product was then purified *via* flash column chromatography on silica gel eluting with 30% EtOAc/hexanes affording **64** (4.90 g, 68% yield over 2 steps) as a white solid.

mp: 138-140 °C

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 6.83 (s, 2H), 3.63 (t, *J* = 8.4 Hz, 1H), 2.80 (m, 1H), 2.66-2.57 (m, 3H), 2.29-2.25 (m, 10H), 2.13 (m, 1H), 1.37 (s, 3H), 0.95 (s, 3H)

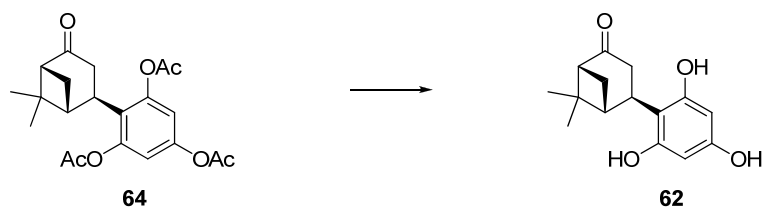
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 212.4, 168.5, 168.4, 149.5, 148.5, 125.0, 114.6, 57.1, 45.3, 42.0, 38.7, 30.6, 26.0, 24.5, 21.8, 20.9

IR (thin film, cm<sup>-1</sup>): 2947, 1769, 1709, 1608, 1427, 1371, 1185, 1122, 1031, 903

HR EI+ Mass Spec. Calculated for C<sub>21</sub>H<sub>24</sub>O<sub>7</sub>: 388.1522, found: 388.1532 (2.6 ppm error)

EI+(*m/z*): 388 (M<sup>+</sup>, 10), 346 (62), 304 (33), 303 (25), 262 (30), 262 (51), 244 (27), 219 (53), 207 (20), 194 (32), 177 (34), 152 (50), 83 (100)

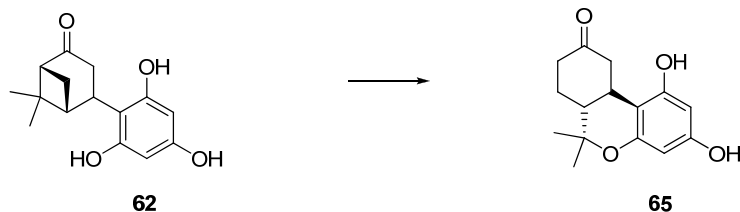
[α]<sub>D</sub><sup>23</sup> -8.0 (*c* 0.010, EtOAc)



To a solution of the triacetate **64** (4.90 g, 12.6 mmol) in 50 mL of MeOH at 0 °C was added KOH (2.48 g, 44.2 mmol) under N<sub>2</sub>. The reaction mixture was stirred at this temperature for an additional 2 h and then quenched with 1 N HCl. MeOH was removed under reduced pressure, and the residue was diluted with EtOAc, washed with brine and dried over MgSO<sub>4</sub>. The crude product was carried on without further purification. An analytical sample could be purified *via* flash column chromatography on silica gel eluting with 50% EtOAc/hexanes affording **62** (3.30 g, 100% yield) as an off-white foam that typically entrains 10-15% ethyl acetate.

<sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>, 300 MHz) δ 5.85 (s, 2H), 3.95 (t, *J* = 8.1 Hz, 1H), 3.67 (dd, *J* = 18.6 Hz, 7.5 Hz, 1H), 2.60 (m, 1H), 2.48-2.35 (m, 3H), 2.14 (t, *J* = 6.0 Hz, 1H), 1.35 (s, 3H), 0.94 (s, 3H)

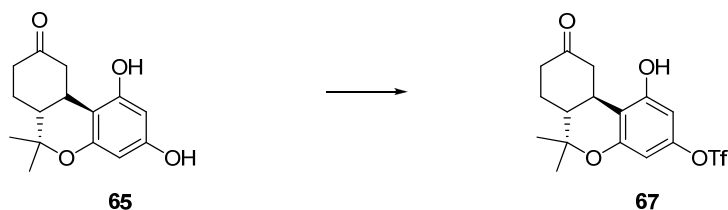
<sup>13</sup>C NMR (MeOH-*d*<sub>4</sub>, 75 MHz) δ 220.2, 158.5, 157.3, 108.9, 95.9, 59.3, 48.8, 43.2, 38.8, 30.0, 26.6, 24.9, 22.4



To a solution of **62** (1.02 g, 3.89 mmol; the mass of pure ketone **62** was 1.20 g; (ethyl acetate was present as an impurity) in 300 mL of MeNO<sub>2</sub> at 0 °C was added TMSOTf (1.76 mL, 9.73 mmol) dropwise. The resulting mixture was stirred for 2.5 h at 0 °C, then quenched with solid K<sub>2</sub>CO<sub>3</sub> and stirred for 45 min at rt. The solids were filtered off and the solvent removed under reduced pressure. Crude **65** was used without further purification in the next step.

<sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>, 300 MHz) δ 5.85 (d, *J* = 2.4 Hz, 1H), 5.76 (d, *J* = 2.4 Hz, 1H), 3.81 (dd, *J* = 15.0 Hz, 3.0 Hz, 1H), 2.75 (m, 1H), 2.47-2.25 (m, 2H), 2.18-2.02 (m, 2H), 1.92 (td, *J* = 12.3 Hz, 2.4 Hz, 1H), 1.51 (m, 1H), 1.42 (s, 3H), 1.08 (s, 3H)

<sup>13</sup>C NMR (MeOH-*d*<sub>4</sub>, 75 MHz) δ 214.6, 158.3, 156.6, 111.2, 104.3, 96.7, 96.6, 77.8, 46.8, 41.5, 36.0, 28.1, 27.9, 19.0



To crude ketone **65** (1.02 g, 3.89 mmol) in 40 mL of CH<sub>2</sub>Cl<sub>2</sub> at 0 °C was added TEA (1.62 mL, 11.7 mmol) followed by dropwise addition of *N*-phenyltrifluoromethanesulfonimide (1.60 g, 4.47 mmol) in 40 mL of CH<sub>2</sub>Cl<sub>2</sub> *via* cannula. The reaction mixture was allowed to warm to room temperature over 12 h, was quenched with 1 N HCl and washed with water. The aqueous layer was back extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with brine and dried over MgSO<sub>4</sub>. The crude product was purified *via* flash column chromatography on silica gel eluting with 20, 30 and 40% EtOAc/hexanes affording **67** (874 mg, 57% yield over 2 steps) as a white semi-solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.39 (d,  $J = 2.4$  Hz, 1H), 6.33 (d,  $J = 2.4$  Hz, 1H), 4.13 (d,  $J = 15$  Hz, 1H), 2.89 (m, 1H), 2.70 (m, 1H), 2.53 (m, 1H), 2.25-1.95 (m, 3H), 1.62-1.49 (m, 4H), 1.29-1.12 (m, 4H)

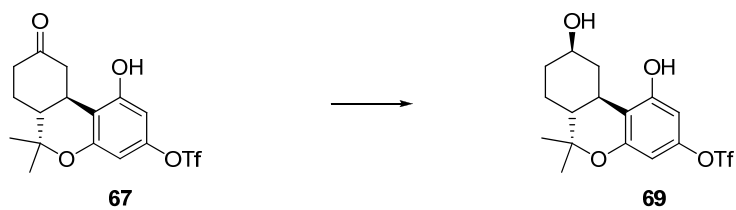
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  215.9, 156.6, 155.6, 148.8, 110.7, 102.3, 100.9, 77.8, 46.9, 44.2, 40.7, 34.7, 27.6, 26.8, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 3415(br), 1617, 1423, 1246, 1211, 1141, 1099

HR EI+ Mass Spec. Calculated for  $\text{C}_{16}\text{H}_{17}\text{F}_3\text{O}_6\text{S}$ : 394.0698, found: 394.0681 (4.2 ppm error)

EI+ ( $m/z$ ): 394 ( $\text{M}^+$ , 13), 279 (28), 270 (72), 243 (69), 225 (80), 207 (100), 195 (70)

$[\alpha]_{\text{D}}^{23}$  -45 ( $c$  0.006,  $\text{CH}_2\text{Cl}_2$ )



To ketone **67** (583 mg, 1.48 mmol) in 15 mL of MeOH at 0 °C was added NaBH<sub>4</sub> (280 mg, 7.40 mmol) in 3 portions over 5 min. The reaction mixture was then stirred for 1 h, quenched with dropwise addition of 1 N HCl and diluted with EtOAc. The organic layer was washed with brine and dried over MgSO<sub>4</sub>. The crude product was then purified *via* flash column chromatography on silica gel eluting with 30% then 40% EtOAc/hexanes affording alcohol **69** and minor alcohol **70** (570 mg, 97% combined yield; the minor diastereomer is easily removed during column chromatography after the subsequent protection) as a white foam.



$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  8.19 (br s, 1H), 6.27 (s, 1H), 6.18 (s, 1H), 3.95 (m, 1H), 3.62 (m, 1H), 2.50-2.42 (m, 2H), 2.18 (m, 1H), 1.91 (m, 1H), 1.51-1.42 (m, 2H), 1.37 (s, 3H), 1.16 (m, 1H), 1.03 (m, 4H)

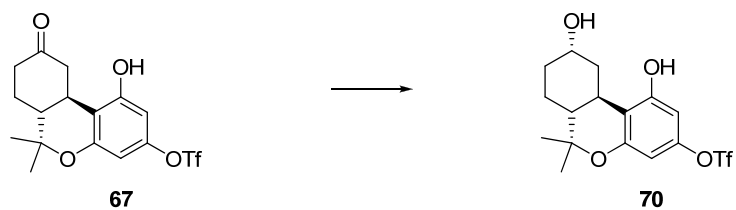
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  156.5, 155.9, 148.3, 119.9, 102.3, 100.6, 77.8, 71.5, 47.7, 37.1, 35.7, 33.3, 27.6, 25.8, 18.9 (C belonging to the triflate was not observed due to its long relaxation time)

IR (thin film,  $\text{cm}^{-1}$ ): 3245(br), 2937, 2873, 1597, 1420, 1245, 1213, 1141, 989, 857

HR EI+ Mass Spec. Calculated for  $\text{C}_{16}\text{H}_{19}\text{F}_3\text{O}_6\text{S}$ : 396.0854, found: 396.0863 (2.1 ppm error)

EI+ ( $m/z$ ): 396 ( $\text{M}^+$ , 79), 378 (45), 336 (57), 335 (100), 186 (29), 69 (71)

$[\alpha]_{\text{D}}^{23}$  -64 ( $c$  0.015,  $\text{CH}_2\text{Cl}_2$ )



To ketone **67** (299 mg, 0.76 mmol) in 8 mL of THF at  $-78^{\circ}\text{C}$  was added a 1 M solution of L-Selectride<sup>®</sup> in THF (3.00 mL, 3.00 mmol). The reaction was maintained at  $-78^{\circ}\text{C}$  for 2 h and then stirred at room temperature for 1 h. The flask was cooled to  $-78^{\circ}\text{C}$  and solid  $\text{NaHCO}_3$  (930 mg, 11.1 mmol) was added followed by dropwise addition of a 30% aqueous solution of  $\text{H}_2\text{O}_2$  (1.60 mL). After the addition of 30%  $\text{H}_2\text{O}_2$  was complete the cooling bath was removed and the reaction mixture was stirred for 1 h at rt. A saturated solution of sodium thiosulfate (5 mL) was added and the reaction mixture was stirred for an additional 30 min. Ether was added and the organic layer was separated, then washed with brine and dried over  $\text{MgSO}_4$ . The crude product was purified *via* flash column chromatography on silica gel eluting with 40% EtOAc/hexanes affording alcohol **70** (269 mg, 90% yield) as a white solid. Alcohol **69** was not observed in the  $^1\text{H}$  NMR at 300 MHz.

mp: 188.5-192.5 °C

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.66 (br s, 1H), 6.30 (d,  $J = 2.5$  Hz, 1H), 6.26 (d,  $J = 2.5$  Hz, 1H), 4.35 (s, 1H), 3.24 (d,  $J = 14.1$  Hz, 1H), 2.93-2.86 (m, 1H), 2.54 (br s, 1H), 1.97 (m, 1H), 1.77-1.68 (m, 2H), 1.56-1.46 (m, 2H), 1.37-1.26 (m, 4H), 0.99 (s, 3H)

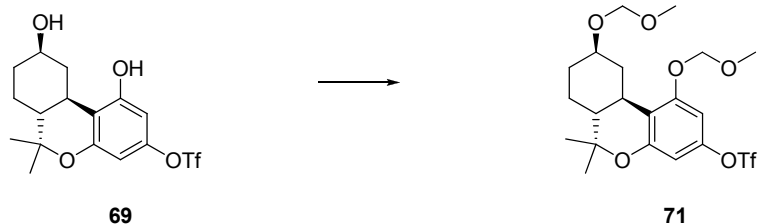
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  156.1, 148.3, 112.8, 102.9, 101.3, 77.7, 67.5, 48.8, 35.3, 33.5, 28.9, 27.2, 22.5, 18.8 (C belonging to the triflate was not observed due to its long relaxation time)

IR (thin film,  $\text{cm}^{-1}$ ): 3210(br), 2938, 1597, 1506, 1419, 1245, 1212, 1140, 1102, 987, 879, 839, 735

HR EI+ Mass Spec. Calculated for  $\text{C}_{16}\text{H}_{19}\text{F}_3\text{O}_6\text{S} - \text{H}_2\text{O}$ : 378.0749, found: 378.0743 (1.6 ppm error)

EI+ ( $m/z$ ): 396 ( $\text{M}^+$ , 8), 378 (64), 335 (56), 309 (31), 202 (14), 151 (42), 101 (39), 92 (19), 69 (100)

$[\alpha]_{\text{D}}^{23}$  -58 ( $c$  0.014,  $\text{CH}_2\text{Cl}_2$ )



Alcohol **69** (430 mg, 1.08 mmol) was dissolved in 10 mL of  $\text{CH}_2\text{Cl}_2$ , was cooled to  $0^\circ\text{C}$  and was treated with DIPEA (1.13 mL, 6.48 mmol) and dropwise addition of MOMCl (492  $\mu\text{L}$ , 6.48 mmol). After 45 min the cooling bath was removed and the reaction mixture was stirred at room temperature for another 1 h 45 min. Saturated  $\text{NaHCO}_3$  was added to quench the reaction and the resulting mixture was diluted with  $\text{Et}_2\text{O}$ . The organic layers were washed with  $\text{CuSO}_4$  and brine, then dried over  $\text{MgSO}_4$ . The crude product was purified *via* flash column chromatography on silica gel eluting with 20%  $\text{EtOAc}$ /hexanes affording **71** (487 mg, 93% yield) as a clear, colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.56 (d,  $J = 2.5$  Hz, 1H), 6.40 (d,  $J = 2.5$  Hz, 1H), 5.19-5.12 (m, 2H), 4.74-4.69 (m, 2H), 3.71 (m, 1H), 3.47 (s, 3H), 3.69 (s, 3H), 3.33 (m, 1H), 2.44 (td,  $J = 11.3$  Hz, 2.4 Hz, 1H), 2.19 (m, 1H), 1.89 (m, 1H), 1.55-1.37 (m, 5H), 1.19-1.03 (m, 5H)

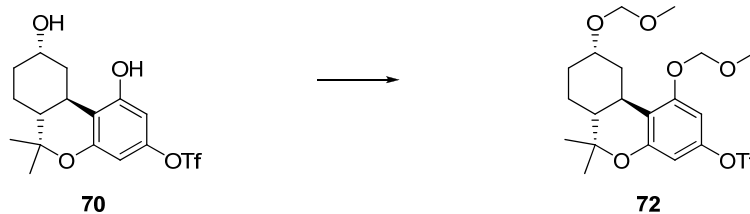
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  157.1, 155.4, 148.5, 114.2, 104.3, 99.5, 94.8, 94.6, 77.8, 75.5, 56.3, 55.1, 48.1, 36.1, 33.7, 33.0, 27.4, 25.9, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 3197, 3105, 2940, 2789, 1603

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{27}\text{F}_3\text{O}_8\text{S}$ : 484.1379, found: 484.1354 (5.0 ppm error)

EI+ ( $m/z$ ): 484 ( $\text{M}^+$ , 7), 379 (33), 378 (100), 335 (25), 245 (19)

$[\alpha]_{\text{D}}^{23}$  -68 ( $c$  0.017,  $\text{CH}_2\text{Cl}_2$ )



Compound **72** was prepared from **70** (247 mg, 0.623 mmol) in 94% yield (284 mg) as a clear, colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.55 (d,  $J = 2.4$  Hz, 1H), 6.42 (d,  $J = 2.4$  Hz, 1H), 5.19-5.12 (m, 2H), 4.81 (d,  $J = 6.8$  Hz, 1H), 6.71 (d,  $J = 6.8$  Hz, 1H), 4.02 (m, 1H), 3.48 (s, 3H), 3.44 (s, 3H), 3.26 (m, 1H), 2.88 (td,  $J = 11.0$  Hz, 2.3 Hz, 1H), 2.04 (m, 1H), 1.71-1.43 (m, 4H), 1.38 (s, 3H), 1.18 (m, 1H), 1.08 (s, 3H)

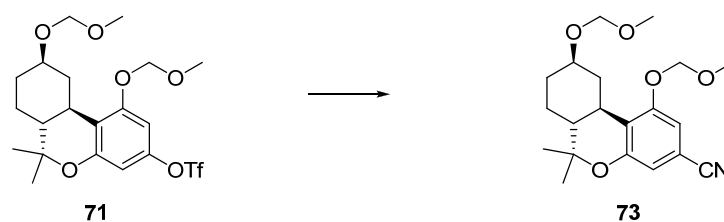
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  157.1, 155.7, 148.4, 115.0, 104.4, 99.5, 94.7, 94.2, 77.9, 70.8, 56.3, 55.2, 48.8, 33.9, 31.3, 29.7, 27.3, 23.1, 19.0

IR (thin film,  $\text{cm}^{-1}$ ): 3198, 2978, 2942, 2827, 2788, 1603

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{27}\text{F}_3\text{O}_8\text{S}$ : 484.1379, found: 484.1354 (5.0 ppm error)

EI+ ( $m/z$ ): 484 ( $\text{M}^+$ , 8), 439 (14), 379 (35), 378 (100), 335 (35), 245 (27), 149 (15), 69 (31)

$[\alpha]_{\text{D}}^{23}$  -62 ( $c$  0.013,  $\text{CH}_2\text{Cl}_2$ )



To triflate **71** (435 mg, 0.90 mmol) was added  $\text{Zn}(\text{CN})_2$  (84 mg, 0.72 mmol),  $\text{Pd}_2(\text{dba})_3$  (82 mg, 0.090 mmol) and  $\text{PPh}_3$  (188 mg, 0.718 mmol) followed by PMHS (44 mg, 10 wt. %) and 27 mL of DMF under an atmosphere of argon. The reaction mixture was further degassed by bubbling argon through the mixture for 15 min. The reaction mixture was heated to 60 °C and stirred for 8 h. The solvent was removed under reduced pressure and the residue was adsorbed onto Celite. The crude product was subjected to flash column chromatography on silica gel eluting with 10%, 20% and 30% EtOAc/hexanes affording **73** as a clear, colorless viscous oil (313 mg, 96% yield).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.90 (d,  $J = 1.6$  Hz, 1H), 6.77 (d,  $J = 1.6$  Hz, 1H), 5.21 (d,  $J = 6.8$  Hz, 1H), 5.16 (d,  $J = 6.8$  Hz, 1H), 4.73 (dd,  $J = 8.0$  Hz, 7.1 Hz, 2H), 3.74 (m, 1H), 3.49 (s, 3H), 3.40-3.30 (m, 4H), 2.49 (td,  $J = 11.4$  Hz, 2.4 Hz, 1H), 2.21 (m, 1H), 1.92 (m, 1H), 1.57-1.39 (m, 5H), 1.20-1.03 (m, 5H)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  156.7, 155.2, 119.8, 118.8, 115.6, 110.9, 108.7, 94.9, 94.5, 77.8, 75.5, 56.4, 55.2, 48.2, 36.1, 34.1, 33.0, 27.5, 25.9, 18.7

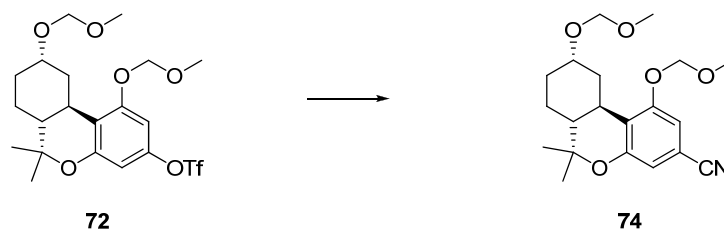
IR (thin film,  $\text{cm}^{-1}$ ): 2939, 2880, 2228, 1565, 1423, 1369, 1336, 1207, 1155, 1103, 1058

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{27}\text{NO}_5$ : 361.1889, found: 361.1880 (2.5 ppm error)

EI+ ( $m/z$ ): 361 ( $\text{M}^+$ , 11), 285 (19), 255 (100), 240 (25), 212 (75), 69 (10)

$[\alpha]_{\text{D}}^{23}$  -78 ( $c$  0.007,  $\text{CH}_2\text{Cl}_2$ )





Nitrile **74** was obtained from **72** (510 mg, 1.05 mmol) in 97% yield (370 mg) as a colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.86 (s, 1H), 6.74 (s, 1H), 5.17 (d,  $J = 6.6$  Hz, 1H), 5.12 (d,  $J = 6.6$  Hz, 1H), 4.79 (d,  $J = 6.8$  Hz, 1H), 4.69 (d,  $J = 6.8$  Hz, 1H), 4.01 (bs, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 3.23 (m, 1H), 2.93 (app t,  $J = 9.6$  Hz, 1H), 2.02 (m, 1H), 1.70 -1.32 (m, 7H), 1.15 (m, 1H), 1.04 (s, 3H)

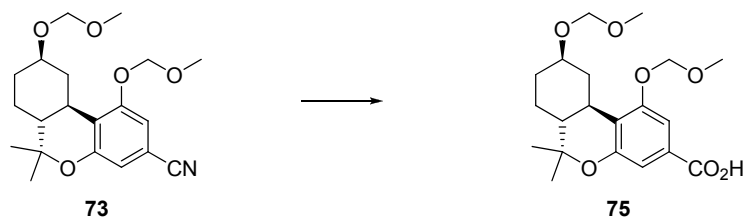
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  156.5, 155.3, 120.6, 118.7, 115.4, 110.4, 108.4, 94.4, 94.0, 77.6, 70.5, 56.2, 55.0, 48.6, 33.7, 31.1, 30.0, 27.1, 23.0, 18.7

IR (thin film,  $\text{cm}^{-1}$ ): 2938, 2229, 1564, 1413, 1339, 1224, 1150, 1101, 1048, 1003

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{27}\text{NO}_5$ : 361.1889, found: 361.1880 (2.5 ppm error)

EI+ ( $m/z$ ): 361 ( $\text{M}^+$ , 7), 284 (16), 255 (100), 212 (63), 77 (22)

$[\alpha]_{\text{D}}^{23}$  -85 ( $c$  0.009,  $\text{CH}_2\text{Cl}_2$ )



To nitrile **73** (52 mg, 0.15 mmol) in a screw cap vial was added MeOH:H<sub>2</sub>O (4:1, 1 mL) and LiOH (61 mg, 1.45 mmol) and the mixture was heated to 70 °C in an oil bath for 3 days. Conc. HCl was added to the reaction mixture and the resultant milky solution was extracted with CHCl<sub>3</sub>, washed with saturated brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Acid **75** was obtained as a clear, colorless oil (50 mg, 91% yield). No purification was necessary.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 7.29 (s, 1H), 7.24 (s, 1H), 5.26 (d, *J* = 6.6 Hz, 1H), 5.20 (d, *J* = 6.6 Hz, 1H), 4.74 (dd, *J* = 9.3 Hz, 6.9 Hz, 2H), 3.76 (m, 1H), 3.51 (s, 3H), 3.47-3.40 (m, 4H), 2.51 (td, *J* = 11.1 Hz, 1.8 Hz, 1H), 2.25-2.18 (m, 1H), 1.90 (m, 1H), 1.60-1.40 (m, 5H), 1.25-1.04 (m, 5H)

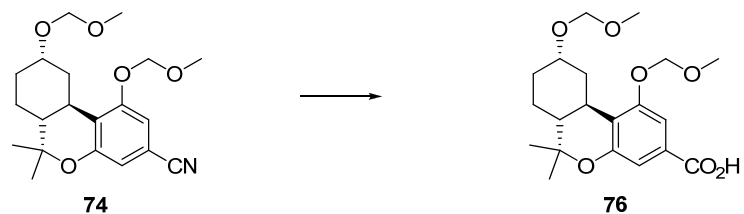
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 171.2, 156.3, 154.8, 128.7, 120.1, 113.7, 106.5, 94.8, 94.5, 77.4, 75.7, 56.4, 55.2, 48.4, 36.2, 34.3, 33.1, 27.6, 26.1, 18.7

IR (thin film, cm<sup>-1</sup>): 2939, 1719, 1690, 1574, 1424, 1375, 1211, 1149, 1100, 1051

HR EI+ Mass Spec. Calculated for C<sub>20</sub>H<sub>28</sub>O<sub>7</sub>: 380.1835, found: 380.1827 (2.1 ppm error)

EI+(*m/z*): 380 (M<sup>+</sup>, 3), 293 (11), 149 (100), 71 (26)

[α]<sub>D</sub><sup>23</sup> -86 (*c* 0.014, CH<sub>2</sub>Cl<sub>2</sub>)



Acid **76** was obtained from **74** (68 mg, 0.19 mmol) in 91% yield (65 mg) as a semi solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  7.28 (d,  $J = 1.7$  Hz, 1H), 7.24 (d,  $J = 1.7$  Hz, 1H), 5.25 (d,  $J = 6.6$  Hz, 1H), 5.19 (d,  $J = 6.6$  Hz, 1H), 4.85 (d,  $J = 6.9$  Hz, 1H), 4.73 (d,  $J = 6.9$  Hz, 1H), 4.04 (br s, 1H), 3.50 (s, 3H), 3.45 (s, 3H), 3.33 (m, 1H), 2.94 (td,  $J = 11.0$  Hz, 2.2 Hz, 1H), 2.04 (m, 1H), 1.70 (m, 1H), 1.60-1.40 (m, 5H), 1.25-1.13 (m, 2H), 1.08 (s, 3H)

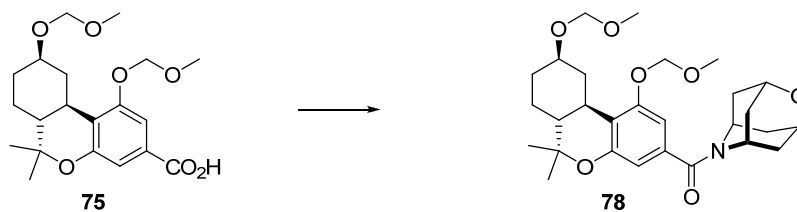
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  171.4, 156.3, 155.0, 128.6, 121.0, 113.7, 106.5, 94.5, 94.0, 77.3, 70.7, 56.4, 55.2, 48.9, 33.8, 31.3, 30.3, 27.4, 23.2, 18.9

IR (thin film,  $\text{cm}^{-1}$ ): 2936, 1688, 1570, 1418, 1296, 1212, 1149, 1046

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{28}\text{O}_7$ : 380.1835, found: 380.1824 (2.9 ppm error)

EI+ ( $m/z$ ): 380 ( $\text{M}^+$ , 15), 274 (100), 259 (24), 231 (56), 191 (10)

$[\alpha]_{\text{D}}^{23}$  -86 ( $c$  0.013,  $\text{CH}_2\text{Cl}_2$ )



To a solution of **75** (30 mg, 0.079 mmol) in 2 mL CH<sub>2</sub>Cl<sub>2</sub> was added amine **77** (30 mg, 0.12 mmol) followed by DMAP (39 mg, 0.32 mmol) and EDCI (30 mg, 0.16 mmol). The flask was sealed with a Teflon cap and stirred overnight at rt. The mixture was diluted with EtOAc, washed with 1 N HCl, brine and dried over MgSO<sub>4</sub>. The crude product was directly adsorbed onto Celite and purified *via* flash column chromatography eluting with 80% EtOAc/hexanes affording amide **78** as a clear, colorless oil (36 mg, 91% yield).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.66 (s, 1H), 6.49 (s, 1H), 5.21 (d,  $J = 6.6$  Hz, 1H), 5.12 (d,  $J = 6.6$  Hz, 1H), 5.05 (br s, 1H), 4.72 (dd,  $J = 9.6$  Hz, 6.9 Hz, 2H), 4.24-4.18 (m, 3H), 3.73 (m, 1H), 3.47 (s, 3H), 3.43-3.34 (m, 4H), 2.47 (td,  $J = 11.2$  Hz, 2.0 Hz, 1H), 2.21-1.75 (m, 10H), 1.57-1.37 (m, 5H), 1.21-1.02 (m, 5H)

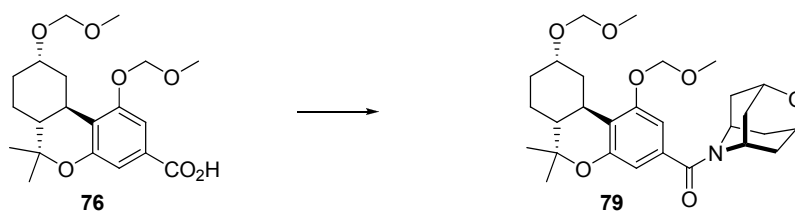
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  169.1, 156.6, 154.8, 135.4, 115.5, 109.4, 103.9, 94.7, 94.5, 77.2, 75.6, 66.7, 56.2, 55.1, 49.0, 48.4, 42.9, 36.3, 35.1, 34.3, 33.9, 33.1, 27.6, 26.0, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 2937, 1626, 1566, 1424, 1370, 1148, 1101, 1048

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{39}\text{NO}_7$ : 501.2727, found: 501.2702 (5.0 ppm error)

EI+ ( $m/z$ ): 501 ( $\text{M}^+$ , 28), 457 (23), 395 (100), 380 (13), 352 (20), 257 (30), 167 (17), 149 (44), 95 (21), 71 (24), 69 (30)

$[\alpha]_{\text{D}}^{23}$  -33 ( $c$  0.011,  $\text{CH}_2\text{Cl}_2$ )



Amide **79** was obtained from **76** (30 mg, 0.079 mmol) in 88% yield (35 mg) as a colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.63 (d,  $J = 1.2$  Hz, 1H), 6.48 (d,  $J = 1.2$  Hz, 1H), 5.19 (d,  $J = 6.6$  Hz, 1H), 5.09 (d,  $J = 6.6$  Hz, 1H), 5.04 (br s, 1H), 4.81 (d,  $J = 6.9$  Hz, 1H), 4.70 (d,  $J = 6.9$  Hz, 1H), 4.25-4.18 (m, 3H), 4.01 (br s, 1H), 3.45 (s, 3H), 3.42 (s, 3H), 3.27 (m, 1H), 2.88 (m, 1H), 2.17-1.74 (m, 9H), 1.71-1.35 (m, 7H), 1.17 (m, 1H), 1.05 (s, 3H)

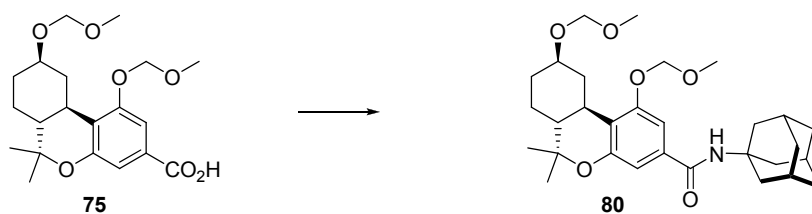
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  169.2, 156.6, 155.0, 135.2, 116.3, 109.4, 103.9, 94.5, 94.0, 77.3, 70.7, 66.8, 56.2, 55.2, 49.1, 42.9, 35.1, 34.3, 34.2, 34.0, 31.4, 29.9, 27.4, 23.2, 19.0

IR (thin film,  $\text{cm}^{-1}$ ): 2937, 1626, 1566, 1424, 1370, 1148, 1101, 1048

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{39}\text{NO}_7$ : 501.2727, found: 501.2710 (3.4 ppm error)

EI+ ( $m/z$ ): 501 ( $\text{M}^+$ , 28), 424 (18), 395 (65), 321 (26), 293 (29), 167 (46), 149 (100), 104 (19), 85 (55), 71 (54), 69 (49)

$[\alpha]_D^{23}$  -67 ( $c$  0.015,  $\text{CH}_2\text{Cl}_2$ )



Amide **80** was obtained from **75** (30 mg, 0.079 mmol) in 90% yield (36 mg) as a colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.06 (d,  $J = 2.0$  Hz, 1H), 6.70 (d,  $J = 2.0$  Hz, 1H), 5.73 (s, 1H), 5.25 (d,  $J = 6.5$  Hz, 1H), 5.18 (d,  $J = 6.5$  Hz, 1H), 4.73 (dd,  $J = 12.5$  Hz, 6.5 Hz, 2H), 3.74 (m, 1H), 3.49 (s, 3H), 3.43-3.39 (m, 4H), 2.49 (td,  $J = 11.3$  Hz, 2.3 Hz, 1H), 2.21 (m, 1H), 2.12-2.08 (m, 9H), 1.91 (m, 1H), 1.73-1.67 (m, 6H), 1.55-1.40 (m, 5H), 1.18-1.04 (m, 5H)

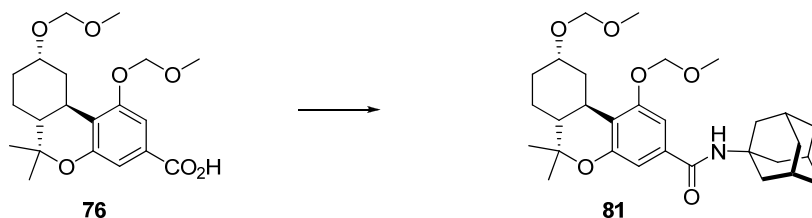
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  166.1, 156.7, 154.5, 135.8, 117.1, 109.0, 104.7, 94.8, 94.5, 77.3, 75.6, 56.5, 55.2, 52.1, 48.5, 41.6, 36.4, 36.3, 34.1, 33.1, 29.5, 27.7, 26.1, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 2907, 1654, 1570, 1522, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{30}\text{H}_{43}\text{NO}_6$ : 513.3090, found: 513.3082 (1.6 ppm error)

EI+ ( $m/z$ ): 513 ( $\text{M}^+$ , 8), 407 (100), 135 (76)

$[\alpha]_D^{23}$  -46 ( $c$  0.017,  $\text{CH}_2\text{Cl}_2$ )



Amide **81** was prepared from **76** (25 mg, 0.066 mmol) in 91% yield (31 mg) as a colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.05 (d,  $J = 1.5$  Hz, 1H), 6.70 (d,  $J = 1.5$  Hz, 1H), 5.73 (br s, 1H), 5.24 (d,  $J = 6.3$  Hz, 1H), 5.16 (d,  $J = 6.3$  Hz, 1H), 4.83 (d,  $J = 6.8$  Hz, 1H), 4.72 (d,  $J = 6.8$  Hz, 1H), 4.04-4.01 (m, 1H), 3.48 (s, 3H), 3.44 (s, 3H), 3.32 (m, 1H), 2.91 (td,  $J = 11.1$  Hz, 2.7 Hz, 1H), 2.11-2.01 (m, 9H), 1.74-1.66 (m, 7H), 1.63-1.42 (m, 4H), 1.39 (s, 3H), 1.15 (m, 1H), 1.06 (s, 3H)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  166.1, 156.7, 154.7, 135.5, 118.0, 109.0, 104.7, 94.5, 94.1, 77.4, 70.7, 56.4, 55.2, 52.1, 49.1, 41.6, 36.4, 34.0, 31.4, 30.0, 29.5, 27.4, 23.2, 19.0

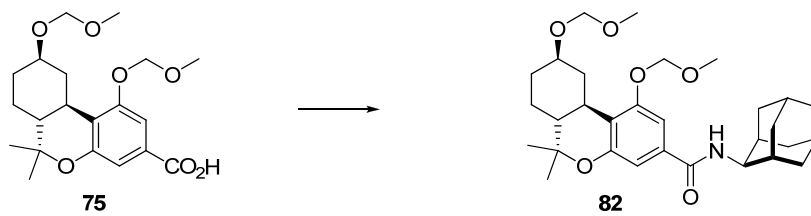
IR (thin film,  $\text{cm}^{-1}$ ): 2907, 2850, 1651, 1570, 1522, 1050

HR EI+ Mass Spec. Calculated for  $\text{C}_{30}\text{H}_{43}\text{NO}_6$ : 513.3090, found: 513.3117 (5.0 ppm error)

EI+ ( $m/z$ ): 513 ( $\text{M}^+$ , 6), 407 (25), 318 (19), 274 (100), 259 (28), 231 (59), 207 (22), 167 (34), 149 (91), 135 (60), 87 (29), 71 (26), 69 (28)

$[\alpha]_D^{23}$  -71 ( $c$  0.018,  $\text{CH}_2\text{Cl}_2$ )





Amide **82** was prepared from **75** (25 mg, 0.066 mmol) in 90% yield (30 mg) as a colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.10 (d,  $J = 1.5$  Hz, 1H), 6.77 (d,  $J = 1.5$  Hz, 1H), 6.34 (d,  $J = 3.0$  Hz, 1H), 5.27 (d,  $J = 6.5$  Hz, 1H), 5.20 (d,  $J = 6.5$  Hz, 1H), 4.73 (dd,  $J = 12.3$  Hz, 6.8 Hz, 2H), 4.20 (br m, 1H), 3.75 (m, 1H), 3.50 (s, 3H), 3.44-3.38 (m, 4H), 2.50 (td,  $J = 11.3$  Hz, 2.3 Hz, 1H), 2.22-2.19 (m, 1H), 2.02-1.98 (m, 2H), 1.94-1.75 (m, 10H), 1.71-1.65 (m, 3H), 1.57-1.51 (td,  $J = 11.5$  Hz, 2.2 Hz, 1H), 1.50-1.41 (m, 4H), 1.19-1.05 (m, 5H)

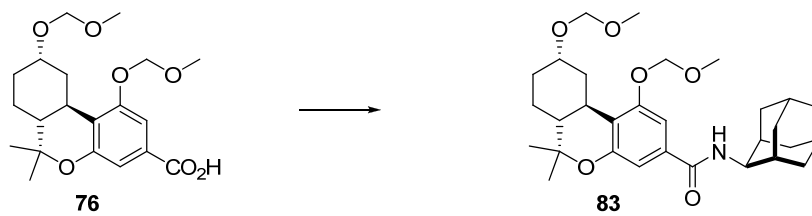
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  166.2, 156.7, 154.6, 135.1, 117.3, 109.0, 104.8, 94.8, 94.6, 77.4, 75.6, 37.5, 37.1, 36.3, 34.1, 33.1, 32.0 (2), 31.9 (2), 27.6, 27.2, 27.1, 26.1, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 2906, 2853, 1653, 1570, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{30}\text{H}_{43}\text{NO}_6$ : 513.3090, found: 513.3096 (1.1 ppm error)

EI+ ( $m/z$ ): 513 ( $\text{M}^+$ , 18), 407 (16), 150 (100), 135 (27)

$[\alpha]_{\text{D}}^{23}$  -48 ( $c$  0.020,  $\text{CH}_2\text{Cl}_2$ )



Amide **83** was prepared from **76** (25 mg, 0.066 mmol) in 91% yield (31 mg) as a colorless oil.

$^1\text{H}$  NMR (MeOH-  $d_4$ , 500 MHz):  $\delta$  7.09 (d,  $J$  = 1.5 Hz, 1H), 6.76 (d,  $J$  = 1.5 Hz, 1H), 6.34 (d,  $J$  = 2.5 Hz, 1H), 5.25 (d,  $J$  = 6.0 Hz, 1H), 5.17 (d,  $J$  = 6.0 Hz, 1H), 4.83 (d,  $J$  = 6.8 Hz, 1H), 4.72 (d,  $J$  = 6.8 Hz, 1H), 4.20 (br m, 1H), 4.03 (br s, 1H), 3.49 (s, 3H), 3.44 (s, 3H), 3.33 (m, 1H), 2.92 (td,  $J$  = 11.0 Hz, 2.5 Hz, 1H), 2.04-1.98 (m, 2H), 1.91-1.74 (m, 10H), 1.72-1.43 (m, 7H), 1.40 (s, 3H), 1.17 (m, 1H), 1.09 (s, 3H)

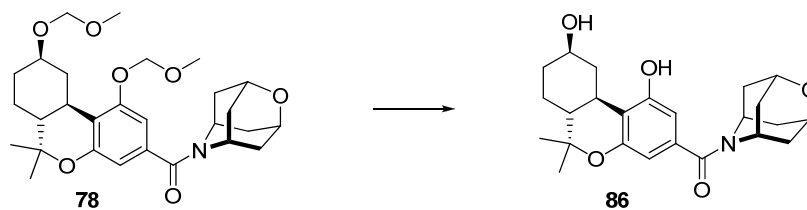
$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 126 MHz):  $\delta$  166.3, 156.7, 154.8, 134.9, 118.2, 109.0, 104.8, 94.6, 94.1, 77.4, 70.6, 56.5, 55.2, 53.5, 49.1, 37.5, 37.1, 34.0, 32.0 (2), 31.9, 31.4, 30.0, 27.4, 27.2, 27.1, 23.2, 19.0

IR (thin film,  $\text{cm}^{-1}$ ): 2908, 2851, 1653, 1570, 1521, 1471, 1049

HR EI+ Mass Spec. Calculated for  $\text{C}_{30}\text{H}_{43}\text{NO}_6$ : 513.3090, found: 513.3102 (2.2 ppm error)

EI+ ( $m/z$ ): 513 ( $\text{M}^+$ , 18), 407 (44), 364 (24), 257 (22), 207 (51), 150 (100), 135 (40), 69 (17)

$[\alpha]_{\text{D}}^{23}$  -68 ( $c$  0.020,  $\text{CH}_2\text{Cl}_2$ )



### General Procedure for Deprotection of MOM Ethers.

To a solution of amide **78** (36 mg, 0.072 mmol) and *n*-BuSH (180  $\mu$ L, 1.68 mmol) in 2 mL of  $\text{CH}_2\text{Cl}_2$  was added  $\text{ZnBr}_2$  (81 mg, 0.36 mmol) all in one portion. The reaction flask was placed in an oil bath and heated at 45  $^\circ\text{C}$  for 8 h. The flask was then cooled to room temperature, diluted with EtOAc and quenched with saturated  $\text{NaHCO}_3$ . The organic layer was washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude product was adsorbed onto Celite and subjected to column chromatography on silica gel using a gradient elution of 2.5, 5, 10% MeOH/ $\text{CH}_2\text{Cl}_2$ . Amide **86** is a white glass obtained in 77% yield (23 mg).

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 7.50 min and 98.6% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  6.33 (d,  $J$  = 1.8 Hz, 1H), 6.29 (d,  $J$  = 1.8 Hz, 1H), 4.96 (br s, 1H), 4.20 (br s, 3H), 3.74 (m, 1H), 3.51 (m, 1H), 2.50 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.18-2.09 (m, 3H), 2.06-2.00 (m, 2H), 1.93-1.80 (m, 5H), 1.46 (td,  $J$  = 11.8 Hz, 2.3 Hz, 1H), 1.42-1.33 (m, 4H), 1.20 (m, 1H), 1.04 (s, 3H), 0.95 (m, 1H)

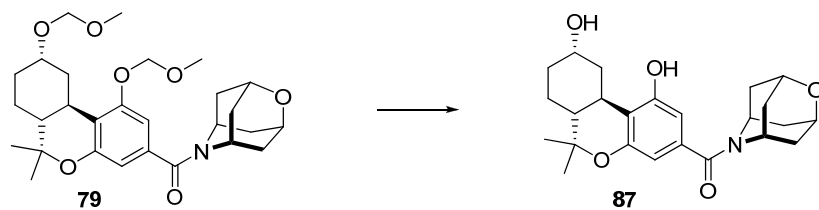
$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 126 MHz):  $\delta$  171.7, 158.4, 156.7, 136.0, 115.4, 107.7, 105.8, 78.4, 71.3, 68.2(2), 51.0, 50.1, 44.8, 39.6, 36.6, 36.0, 35.9, 35.2, 35.1, 28.1, 27.2, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3454(br), 2932, 1738, 1727, 1604, 1572, 1441, 1381, 1240, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{24}\text{H}_{31}\text{NO}_5$ : 413.2202, found: 413.2214 (2.8 ppm error)

EI+ ( $m/z$ ): 413 ( $\text{M}^+$ , 100), 395 (26), 352 (20), 275 (30), 149 (56)

$[\alpha]_{\text{D}}^{23}$  -93 ( $c$  0.007, MeOH)



Compound **87** was prepared from **79** (15 mg, 0.030 mmol) in 89% yield (11 mg) as a white glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 16.47 min and 98.7% chemical purity.

$^1\text{H}$  NMR (MeOH-  $d_4$ , 500 MHz): 6.32 (d,  $J$  = 1.8 Hz, 1H), 6.28 (d,  $J$  = 1.8 Hz, 1H), 4.96 (br s, 1H), 4.20 (br m, 3H), 4.13 (br m, 1H), 3.42-3.37 (m, 1H), 3.00 (td,  $J$  = 11.3, 2.3 Hz, 1H), 2.18-2.10 (m, 2H), 2.06-1.99 (m, 2H), 1.95-1.81 (m, 5H) 1.68-1.60 (m, 2H), 1.56-1.46 (m, 2H), 1.36 (s, 3H), 1.19 (m, 1H), 1.08 (s, 3H)

$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 126 MHz):  $\delta$  171.8, 158.4, 156.9, 135.8, 116.2, 107.7, 105.8, 78.2, 68.2 (2), 67.5, 51.0, 50.6, 44.8, 37.4, 36.0, 35.9, 35.2 (2), 34.2, 30.6, 27.9, 23.7, 19.3

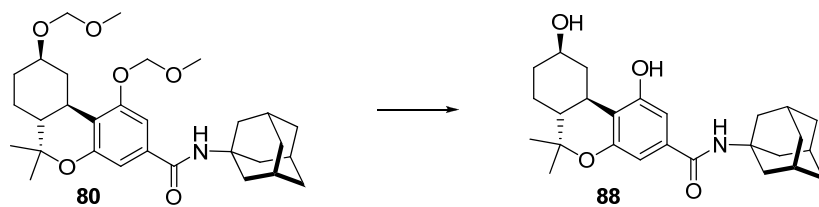
IR (thin film,  $\text{cm}^{-1}$ ): 3454(br), 1642, 1442, 1382, 1194, 1104, 1060

HR EI+ Mass Spec. Calculated for  $\text{C}_{24}\text{H}_{31}\text{NO}_5$ : 413.2202, found: 413.2214 (2.8 ppm error)

EI+ ( $m/z$ ): 413 ( $\text{M}^+$ , 10), 149 (51), 142 (100), 109 (73), 101 (95)

$[\alpha]_{\text{D}}^{23}$  -69 ( $c$  0.005, MeOH)





Amide **88** was prepared from **80** (15 mg, 0.029 mmol) in 89% yield (11 mg) as a colorless oil.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 6.70 min and 98.6% chemical purity.

$^1\text{H}$  NMR (MeOH-  $d_4$ , 300 MHz):  $\delta$  7.21 (br s, 1H), 6.70 (d,  $J$  = 1.8 Hz, 1H), 6.65 (d,  $J$  = 1.8 Hz, 1H), 3.75 (m, 1H), 3.51 (m, 1H), 2.49 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.15-2.05 (m, 10H), 1.90 (m, 1H), 1.78-1.72 (m, 6H), 1.50-1.12 (m, 6H), 1.03 (s, 3H), 0.94 (m, 1H)

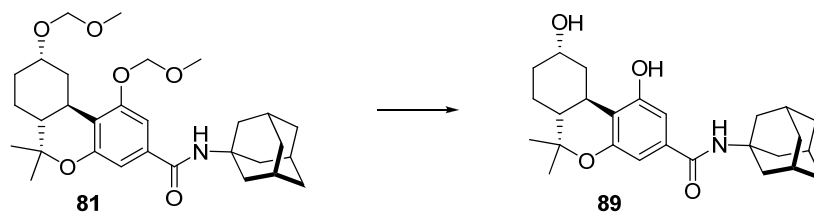
$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 126 MHz):  $\delta$  170.3, 158.1, 156.3, 135.7, 116.9, 108.7, 106.9, 78.2, 71.2, 56.1, 50.1, 39.5, 38.6, 38.3, 36.6, 35.2, 33.0, 32.7, 28.7, 28.1, 27.1, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3447(br), 2909, 2854, 1636, 1555, 1451, 1366, 1275, 1112, 1056

HR EI+ Mass Spec. Calculated for  $\text{C}_{26}\text{H}_{35}\text{NO}_4\text{-H}_2\text{O}$ : 407.2460, found: 407.2459 (0.4 ppm error)

EI+ ( $m/z$ ): 407 ( $\text{M}^+$ , 5), 207(37), 163(17), 150(40), 149(19), 134(16), 105(56), 91(20), 82(86), 80(100), 77(27), 69(19)

$[\alpha]_{\text{D}}^{23}$  -42 ( $c$  0.008, MeOH)



Amide **89** was prepared from **81** (38 mg, 0.074 mmol) in 92% yield (29 mg) as a colorless oil.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 7.00 min and 98.4% chemical purity.

$^1\text{H}$  NMR (MeOH-  $d_4$ , 300 MHz):  $\delta$  6.61 (d,  $J$  = 1.8 Hz, 1H), 6.59 (d,  $J$  = 1.8 Hz, 1H), 4.13 (m, 1H), 3.40 (m, 1H), 2.97 (td,  $J$  = 11.2 Hz, 7.5 Hz, 1H), 2.15-2.05 (m, 10H), 1.93 (m, 1H), 1.75 (br s, 6H), 1.70-1.42 (m, 4H), 1.36 (m, 3H), 1.17 (m, 1H), 1.07 (s, 3H)

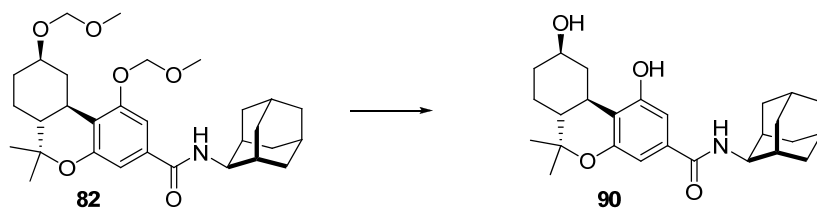
$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 126 MHz):  $\delta$  170.1, 158.0, 156.4, 136.4, 117.4, 108.6, 106.9, 78.0, 67.5, 53.3, 50.6, 42.3, 37.5, 37.4, 34.1, 31.0, 30.7, 27.9, 23.7, 19.3

IR (thin film,  $\text{cm}^{-1}$ ): 3393(br), 2986, 2907, 2850, 1636, 1577, 1420, 1359, 1247, 1134, 1046

HR EI+ Mass Spec. Calculated for  $\text{C}_{26}\text{H}_{35}\text{NO}_4$ : 425.2566, found: 425.2545 (5.0 ppm error)

EI+( $m/z$ ): 425 ( $\text{M}^+$ , 4), 207(48), 192(79), 163(32), 149(33), 105(83), 103(100), 102(28), 87(20), 83(22), 77(36), 69(22)

$[\alpha]_{\text{D}}^{23}$  -78 ( $c$  0.012, MeOH)



Amide **90** was prepared from **82** (17 mg, 33.1  $\mu\text{mol}$ ) in 91% yield (13 mg) as a colorless oil.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 6.90 min and 98.9% chemical purity.

$^1\text{H}$  NMR (MeOH-  $d_4$ , 500 MHz):  $\delta$  6.69 (d,  $J$  = 1.8 Hz, 1H), 6.64 (d,  $J$  = 1.8 Hz, 1H), 4.06 (br s, 1H), 3.74 (m, 1H), 3.51 (m, 1H), 2.49 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.12 (m, 1H), 2.06-2.00 (m, 4H), 1.95-1.79 (m, 9H), 1.69-1.63 (m, 2H), 1.49-1.33 (m, 5H), 1.20 (m, 1H), 1.04 (s, 3H), 0.95 (m, 1H)

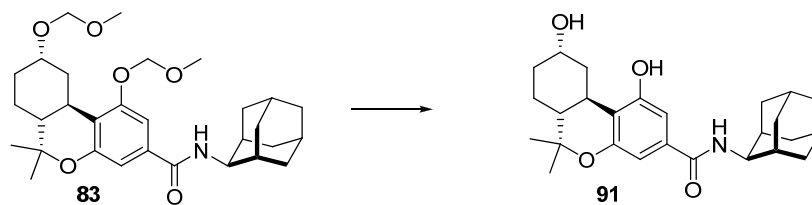
$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 126 MHz):  $\delta$  170.3, 158.1, 156.3, 135.7, 117.0, 108.8, 106.9, 78.2, 71.3, 56.1, 50.1, 39.6, 38.6, 38.3, 36.6, 35.2, 33.0, 32.8, 28.7, 28.1, 27.1, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3365(br), 2907, 2854, 1733, 1717, 1576, 1507, 1055

HR EI+ Mass Spec. Calculated for  $\text{C}_{26}\text{H}_{35}\text{NO}_4$ : 425.2566, found: 425.2555 (2.6 ppm error)

EI+ ( $m/z$ ): 425 ( $\text{M}^+$ , 6), 207(45), 163(40), 149(64), 105(100), 95(22), 91(18), 77(45), 73(51), 69(15)

$[\alpha]_{\text{D}}^{23}$  -71 ( $c$  0.008, MeOH)



Amide **91** was prepared from **83** (30 mg, 58  $\mu$ mol) in 90% yield (22 mg) as a colorless oil.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 6.33 min and 97.7% chemical purity.

$^1\text{H}$  NMR (MeOH-  $d_4$ , 300 MHz):  $\delta$  6.68 (d,  $J$  = 1.8 Hz, 1H), 6.63 (d,  $J$  = 1.8 Hz, 1H), 4.13 (m, 1H), 4.07 (br s, 1H), 3.42 (m, 1H), 2.99 (td,  $J$  = 11.0 Hz, 2.5 Hz, 1H), 2.08-1.79 (m, 13H), 1.72-1.42 (m, 6H), 1.37 (s, 3H), 1.18 (m, 1H), 1.09 (s, 3H)

$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 126 MHz):  $\delta$  170.3, 158.2, 156.6, 135.4, 117.7, 108.7, 107.0, 78.1, 67.5, 56.0, 49.2, 38.6, 38.3, 37.3, 34.1, 33.0, 32.8, 30.7, 28.8, 27.9, 23.7, 19.3

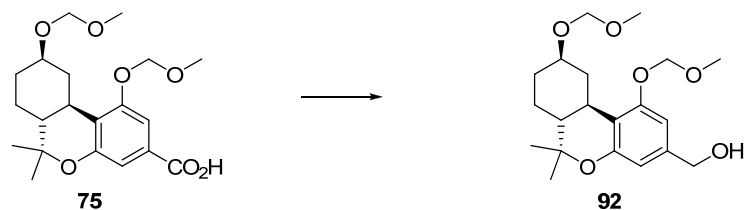
IR (thin film,  $\text{cm}^{-1}$ ): 3314(br), 2982, 2909, 2846, 1651, 1574, 1449, 1375, 1242, 1131, 1046

HR EI+ Mass Spec. Calculated for  $\text{C}_{26}\text{H}_{35}\text{NO}_4$ : 425.2566, found: 425.2558 (2.0 ppm error)

EI+ ( $m/z$ ): 425 ( $\text{M}^+$ , 1), 207(23), 192(55), 163(26), 150(14), 149(17), 105(100), 103(82), 91(22), 87(25), 69(16)

$[\alpha]_{\text{D}}^{23}$  -77 ( $c$  0.011, MeOH)





To carboxylic acid **75** (12 mg, 0.032 mmol) in 0.1 mL THF was added excess  $\text{BH}_3 \cdot \text{THF}$  (100  $\mu\text{L}$ , 1 mmol, 1 M) at 0 °C and the mixture was allowed to warm to room temperature overnight. 6 N HCl was added slowly and carefully at 0 °C and the mixture was diluted with  $\text{CHCl}_3$ . The organic layers were washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude product was purified *via* flash column chromatography on silica gel using 50% EtOAc/hexanes as the eluent which resulted in alcohol **92** (10 mg, 88% yield) as a clear, colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  6.63 (s, 1H), 6.50 (s, 1H), 5.21 (d,  $J = 6.3$  Hz, 1H), 5.16 (d,  $J = 6.3$  Hz, 1H), 4.72 (dd,  $J = 13.3$  Hz, 6.8 Hz, 2H), 4.57 (br s, 2H), 3.74 (m, 1H), 3.50 (s, 3H), 3.44-3.39 (m, 4H), 2.47 (td,  $J = 11.3$  Hz, 2.5 Hz, 1H), 2.20 (m, 1H), 1.91 (m, 1H), 1.56-1.40 (m, 2H), 1.39 (s, 3H), 1.18-1.06 (m, 2H), 1.04 (s, 3H)

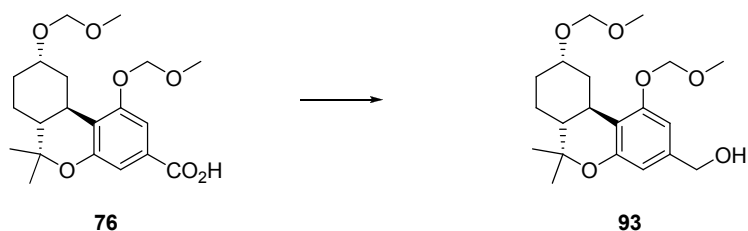
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  156.7, 154.9, 140.8, 113.3, 109.8, 104.2, 94.8, 94.4, 76.9, 75.7, 65.2, 56.3, 55.2, 48.6, 36.5, 33.9, 33.2, 27.7, 26.1, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 3409(br), 2918, 2849, 1577, 1431, 1056, 1042

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{30}\text{O}_6$ : 366.2042, found: 366.2035 (2.0 ppm error)

EI+ ( $m/z$ ): 366 ( $\text{M}^+$ , 26), 260 (100), 245 (28), 217 (34), 177 (10)

$[\alpha]_{\text{D}}^{23}$  -66 ( $c$  0.012,  $\text{CH}_2\text{Cl}_2$ )



Alcohol **93** was prepared from **76** (12 mg, 0.032 mmol) in 88% yield (10 mg) as a colorless oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.61 (d,  $J = 1.5$  Hz, 1H), 6.50 (s, 1H), 5.17 (d,  $J = 6.8$  Hz, 1H), 5.14 (d,  $J = 6.8$  Hz, 1H), 4.84 (d,  $J = 6.8$  Hz, 1H), 4.72 (d,  $J = 6.8$  Hz, 1H), 4.56 (br s, 2H), 4.02 (m, 1H), 3.48 (s, 3H), 3.43 (s, 3H), 3.32 (m, 1H), 2.88 (td,  $J = 11.1$  Hz, 2.5 Hz, 1H), 2.02 (m, 1H), 1.71-1.42 (m, 4H), 1.38 (s, 3H), 1.17 (ddd,  $J = 13.8$  Hz, 11.5 Hz, 2.3 Hz, 1H), 1.08 (s, 3H)

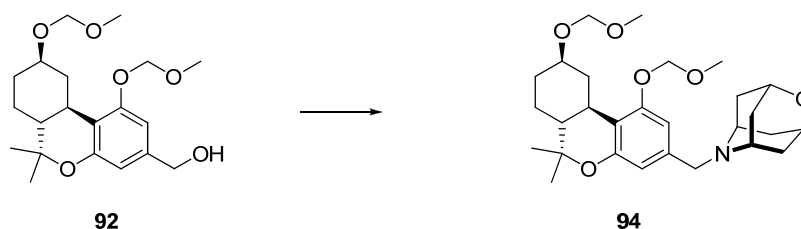
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  156.7, 155.1, 140.6, 114.1, 109.8, 104.2, 94.4, 94.1, 76.9, 70.9, 65.2, 56.2, 55.2, 49.2, 34.1, 31.4, 29.8, 27.5, 23.3, 18.9

IR (thin film,  $\text{cm}^{-1}$ ): 3400(br), 2955, 1620, 1579, 1432, 1367 1186, 1085, 925

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{30}\text{O}_6$ : 366.2042, found: 366.2029 (3.7 ppm error)

EI+ ( $m/z$ ): 366 ( $\text{M}^+$ , 21), 266 (100), 245 (19), 217 (38)

$[\alpha]_{\text{D}}^{23}$  -94 ( $c$  0.014,  $\text{CH}_2\text{Cl}_2$ )



Alcohol **92** (55 mg, 0.15 mmol) was dissolved in 2 mL of THF under N<sub>2</sub>, was cooled to -40 °C and was treated with NEt<sub>3</sub> (125 μL, 0.90 mmol) and MsCl (50 μL, 0.65 mmol). The reaction mixture was allowed to stir at this temperature for 45 min then was warmed to 0 °C and stirred for an additional 30 min. A solution of LiBr (130 mg, 1.50 mmol) in 2 mL of THF was added *via* cannula and the reaction mixture was allowed to warm to room temperature and was stirred for 4 h. The reaction mixture was quenched with ice cold saturated NaHCO<sub>3</sub>, extracted with Et<sub>2</sub>O, washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude bromide and amine **77** (24 mg, 0.17 mmol) were dissolved in 1 mL of DMF under N<sub>2</sub>. K<sub>2</sub>CO<sub>3</sub> (124 mg, 0.90 mmol) was added and the mixture was stirred overnight. The solvent was removed under vacuum then diluted with EtOAc, washed with water, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was subjected to column chromatography on silica gel eluting with 50% then 80% EtOAc/hexanes affording amine **94** (55 mg, 75% yield over 2 steps) as a clear, colorless oil.

$^1\text{H}$  NMR (MeOH-  $d_4$ , 300 MHz):  $\delta$  6.70 (d,  $J$  = 1.5 Hz, 1H), 6.47 (d,  $J$  = 1.5 Hz, 1H), 5.21 (d,  $J$  = 6.5 Hz, 1H), 5.16 (d,  $J$  = 6.5 Hz, 1H), 4.71 (s, 2H), 4.22-4.06 (m, 3H), 3.80 (s, 2H), 3.78-3.67 (m, 1H), 3.51-3.43 (m, 4H), 3.37 (s, 3H), 3.06-3.00 (m, 2H), 2.49 (td,  $J$  = 11.3 Hz, 2.4 Hz, 1H), 2.24-2.03 (m, 5H), 1.96-1.85 (m, 5H), 1.52-1.36 (m, 5H), 1.20 (td,  $J$  = 12.6 Hz, 3.5 Hz, 1H), 1.02 (s, 3H)

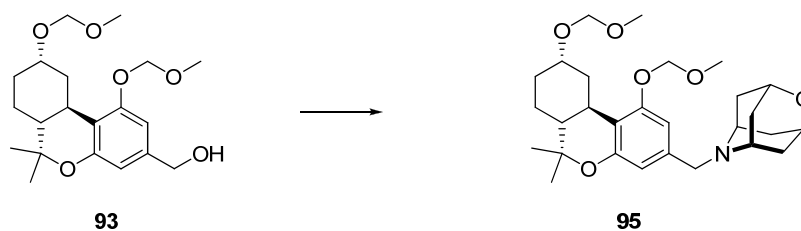
$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 126 MHz):  $\delta$  158.0, 156.0, 114.5, 112.9, 107.7, 95.9, 95.8, 77.9, 77.4, 68.9, 57.7, 56.6, 55.5, 50.9, 50.3, 38.2, 35.2, 34.4, 33.5, 32.8, 28.1, 27.1, 19.0

IR (thin film,  $\text{cm}^{-1}$ ): 2930, 1573, 1429, 1335, 1154, 1106, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{41}\text{NO}_6$ : 487.2934, found: 487.2950 (3.3 ppm error)

EI+ ( $m/z$ ): 487 ( $\text{M}^+$ , 61), 364 (19), 258 (100), 215 (62), 152 (35), 95 (51), 69 (73)

$[\alpha]_{\text{D}}^{23}$  -60 ( $c$  0.029, MeOH)



Amine **95** was prepared from **93** (12 mg, 0.033 mmol) in 72% yield over the 2 steps (12 mg) as a colorless oil.

$^1\text{H}$  NMR (MeOH-  $d_4$ , 500 MHz):  $\delta$  6.68 (d,  $J$  = 1.3 Hz, 1H), 6.46 (d,  $J$  = 1.3 Hz, 1H), 5.17 (dd,  $J$  = 13.8 Hz, 6.8 Hz, 2H), 4.82 (d,  $J$  = 6.5 Hz, 1H), 4.70 (d,  $J$  = 6.5 Hz, 1H), 4.09 (br s, 2H), 3.99 (m, 1H), 3.81 (s, 2H), 3.46 (s, 3H), 3.42 (s, 3H), 3.35 (m, 1H), 3.04 (br s, 2H), 2.87 (td,  $J$  = 11.1 Hz, 2.2 Hz, 1H), 2.05 (m, 5H), 1.92-1.86 (m, 4H), 1.70 (m, 1H), 1.60 (m, 1H), 1.53-1.39 (m, 2H), 1.35 (s, 3H), 1.15 (ddd,  $J$  = 13.8 Hz, 11.6 Hz, 2.1 Hz, 1H), 1.04 (s, 3H)

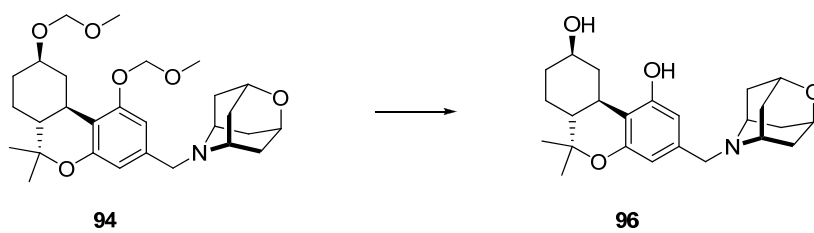
$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 126 MHz):  $\delta$  158.0, 156.2, 145.3, 118.4, 112.9, 112.2, 107.7, 95.7, 95.3, 77.8, 72.6, 68.9, 57.8, 56.6, 55.6, 50.9, 50.7, 35.5, 32.9, 32.4, 31.1, 27.9, 24.3, 19.2

IR (thin film,  $\text{cm}^{-1}$ ): 2927, 1573, 1462, 1428, 1051

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{41}\text{NO}_6$ : 487.2934, found: 487.2919 (3.1 ppm error)

EI+( $m/z$ ): 487 ( $\text{M}^+$ , 7), 277 (23), 258 (29), 149 (83), 69 (100)

$[\alpha]_D^{23}$  -72 ( $c$  0.017, MeOH)



Amine **96** was prepared from **94** (33 mg, 0.068 mmol) in 81% yield (17 mg) as a white glass.

HPLC (0.10 cm x 25 cm Luna C8(2) 5 $\mu$ , 20 - 60% MeCN in water (both containing 0.1% HCO<sub>2</sub>H) over 30 min, 3 mL/min, UV detection at 280 nm) 8.56 min and 95.1% chemical purity.

<sup>1</sup>H (MeOH- *d*<sub>4</sub>, 500 MHz):  $\delta$  6.35 (d, *J* = 1.5 Hz, 1H), 6.25 (d, *J* = 1.5 Hz, 1H), 4.07 (br s, 2H), 3.77-3.70 (m, 3H), 3.53 (m, 1H), 3.00 (br s, 2H), 2.44 (td, *J* = 11.1 Hz, 2.2 Hz, 1H), 2.13-2.04 (m, 5H), 1.91-1.83 (m, 5H), 1.42-1.31 (m, 5H), 1.28 (m, 1H), 1.02 (s, 3H), 0.93 (m, 1H)

<sup>13</sup>C (MeOH- *d*<sub>4</sub>, 126 MHz):  $\delta$  170.3, 156.1, 139.5, 112.3, 110.0, 109.1, 77.7, 71.4, 69.2, 57.8, 50.6, 50.3, 39.9, 36.7, 35.1, 32.9, 28.2, 27.2, 19.1

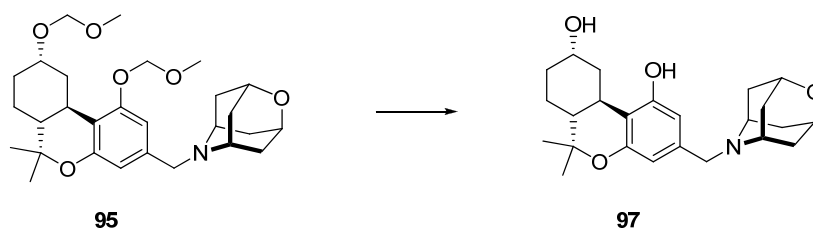
IR (thin film, cm<sup>-1</sup>): 3301(br), 2976, 2934, 2856, 1576, 1427, 1056, 997

HR EI+ Mass Spec. Calculated for C<sub>24</sub>H<sub>33</sub>NO<sub>4</sub>: 399.2410, found: 399.2427 (4.4 ppm error)

EI+(*m/z*): 399 (M<sup>+</sup>, 100), 340 (39), 261 (50), 152 (26)

$[\alpha]_{\text{D}}^{23}$  -108 (*c* 0.0104, MeOH)





Amine **97** was prepared from **95** (20 mg, 0.041 mmol) in 73% yield (12 mg) as a colorless oil.

HPLC (0.10 cm x 25 cm Luna C8(2) 5 $\mu$ , 20 - 60% MeCN in water (both containing 0.1% HCO<sub>2</sub>H) over 30 min, 3 mL/min, UV detection at 280 nm) 7.59 min and 96.9% chemical purity.

<sup>1</sup>H NMR (MeOH- *d*<sub>4</sub>, 500 MHz):  $\delta$  6.48 (d, *J* = 1.8 Hz, 1H), 6.45 (d, *J* = 1.8 Hz, 1H), 4.35 (d, *J* = 13.0 Hz, 1H), 4.33 (d, *J* = 13.0 Hz, 1H), 4.16-4.10 (m, 3H), 3.72 (br s, 2H), 3.38 (m, 1H), 2.96 (td, *J* = 11.3 Hz, 2.8 Hz, 1H), 2.32-2.24 (m, 4H), 2.22-2.15 (m, 4H), 1.93 (m, 1H), 1.68-1.42 (m, 4H), 1.35 (s, 3H), 1.15 (ddd, *J* = 14.0 Hz, 11.8 Hz, 2.3 Hz, 1H), 1.07 (s, 3H)

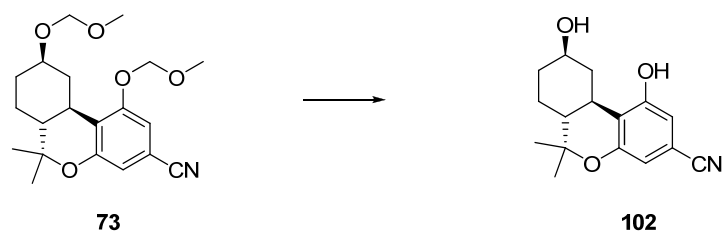
<sup>13</sup>C NMR (MeOH- *d*<sub>4</sub>, 126 MHz):  $\delta$  158.7, 157.3, 130.0, 116.0, 111.9, 110.1, 78.2, 67.4, 65.9, 56.6, 53.8, 50.6, 37.3, 34.1, 31.6, 30.5, 27.9, 23.6, 19.3

IR (thin film, cm<sup>-1</sup>): 3334(br), 2980, 2934, 2874, 1576, 1426, 1336, 1045, 999

HR EI+ Mass Spec. Calculated for C<sub>24</sub>H<sub>33</sub>NO<sub>4</sub>: 399.2410, found: 399.2418 (2.1 ppm error)

EI+(*m/z*): 399 (M<sup>+</sup>, 47), 207 (100)

$[\alpha]_D^{23}$  -95 (*c* 0.006, MeOH)



To nitrile **73** (132 mg, 0.365 mmol) in 3.5 mL of CH<sub>2</sub>Cl<sub>2</sub> at rt was added *n*-BuSH (390 μL, 3.65 mmol) followed by ZnBr<sub>2</sub> (544 mg, 2.41 mmol) all at once. The reaction mixture was stirred for 15 min then diluted with EtOAc, washed with saturated NaHCO<sub>3</sub>, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was subjected to flash column chromatography on silica gel eluting with 50% then 80% EtOAc/hexanes resulting in nitrile **102** (90 mg, 90% yield) as a white solid.

mp: 212.1 °C (dec.)

$^1\text{H}$  NMR (MeOH-  $d_4$ , 300 MHz):  $\delta$  6.55 (s, 2H), 4.62 (br s, 1H), 3.75 (m, 1H), 3.48 (m, 1H), 2.50 (td,  $J$  = 11.2 Hz, 2.4 Hz, 1H), 2.13 (m, 1H), 1.90 (m, 1H), 1.52-1.31 (m, 5H), 1.19 (m, 1H), 1.03 (s, 3H), 0.95 (m, 1H)

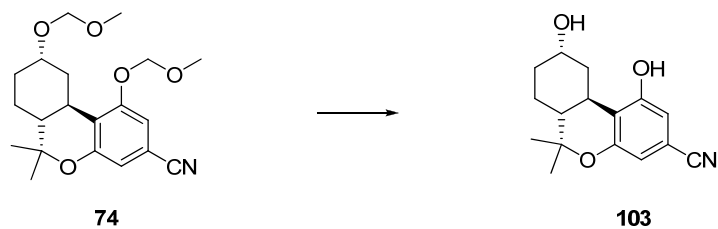
$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 75 MHz):  $\delta$  158.7, 157.0, 119.8, 119.6, 113.6, 111.3, 110.6, 78.8, 71.1, 49.7, 39.2, 36.4, 35.2, 28.0, 27.0, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3234(br), 2982, 2972, 2864, 2224, 1711, 1568, 1424, 1344, 1270, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{16}\text{H}_{19}\text{NO}_3$ : 273.1365, found: 273.1360 (1.8 ppm error)

EI+ ( $m/z$ ): 273 ( $\text{M}^+$ , 72), 240 (53), 212 (100), 186 (18), 69 (36)

$[\alpha]_{\text{D}}^{23}$  -153 ( $c$  0.010, MeOH)



Nitrile **103** was prepared from **74** (127 mg, 0.351 mmol) in 76% yield (73 mg) as a fluffy white solid.

mp: 192.5-195.0 °C

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 6.53 (s, 2H), 4.13 (br s, 1H), 3.41-3.29 (m, 2H), 3.00 (td, *J* = 10.9 Hz, 2.6 Hz, 1H), 1.93 (m, 1H), 1.70-1.44 (m, 3H), 1.37 (s, 3H), 1.17 (ddd, *J* = 13.7 Hz, 11.6 Hz, 2.1 Hz, 1H), 1.07 (s, 3H)

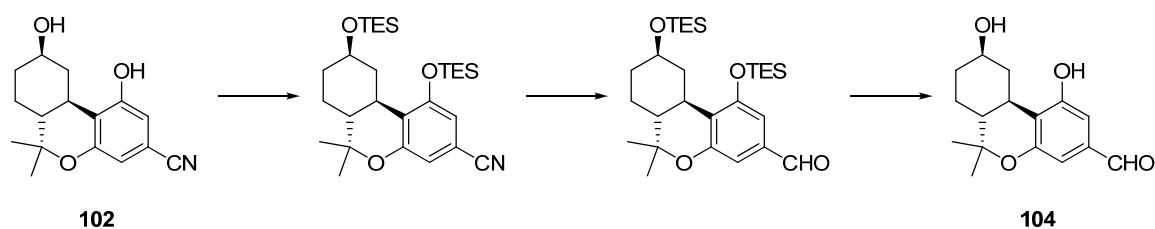
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz): δ 158.8, 157.3, 120.5, 119.9, 113.5, 111.1, 110.6, 78.6, 67.3, 50.2, 37.0, 34.0, 30.8, 27.7, 23.6, 19.2

IR (thin film, cm<sup>-1</sup>): 3435(br), 3135, 2932, 2234, 1736, 1575, 1421, 1344, 1284, 1064

HR EI+ Mass Spec. Calculated for C<sub>16</sub>H<sub>19</sub>NO<sub>3</sub>: 273.1365, found: 273.1378 (4.7 ppm, error)

EI+(*m/z*): 273 (M+, 12), 255 (40), 212 (100), 149 (24)

[α]<sub>D</sub><sup>23</sup> -101.6° (*c* 0.010, MeOH)



To an ice cold solution of nitrile **102** (140 mg, 0.51 mmol) in 5 mL of  $\text{CH}_2\text{Cl}_2$  was added DIPEA (460  $\mu\text{L}$ , 2.56 mmol) followed by dropwise addition of TESCl (300  $\mu\text{L}$ , 1.31 mmol). The reaction mixture was stirred for 20 min, quenched with ice cold saturated  $\text{NaHCO}_3$ , diluted with  $\text{Et}_2\text{O}$ , washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude nitrile was dissolved in 5 mL of  $\text{CH}_2\text{Cl}_2$ , cooled to  $-78^\circ\text{C}$  and stirred for 10 min. DIBAL in PhMe (1.10 mL, 1.32 mmol, 1.2 M) was added dropwise and the resulting mixture was stirred for 1 h. Excess DIBAL was quenched with acetone at  $-78^\circ\text{C}$  and the reaction mixture was stirred with saturated Rochelle's salt at room temperature until the biphasic mixture was clear. EtOAc was added and the organic layer was separated, washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude product was purified on a plug of silica gel eluting with 5% EtOAc/hexanes with 2% TEA present. The silylated aldehyde was dissolved in 5 mL of THF, treated with TBAF (550 mg, 1.74 mmol) at rt and stirred until the reaction was shown to be complete by TLC analysis. Solid  $\text{CaCO}_3$  was added to the flask and stirred for 15 min. EtOAc was added and the organic layer was separated, washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude product was purified *via* flash column chromatography on silica gel eluting with 50% then 80% EtOAc/hexanes resulting in aldehyde **104** (44 mg, 61% yield over 3 steps) as a white foam.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  9.76 (s, 1H), 6.85 (d,  $J = 1.4$  Hz, 1H), 6.79 (d,  $J = 1.4$  Hz, 1H), 3.96 (m, 1H), 3.65 (m, 1H), 2.55 (td,  $J = 11.1$  Hz, 2.1 Hz, 1H), 2.21 (m, 1H), 1.92 (m, 1H), 1.57-1.41 (m, 5H), 1.25-1.15 (m, 2H), 1.07 (s, 3H)

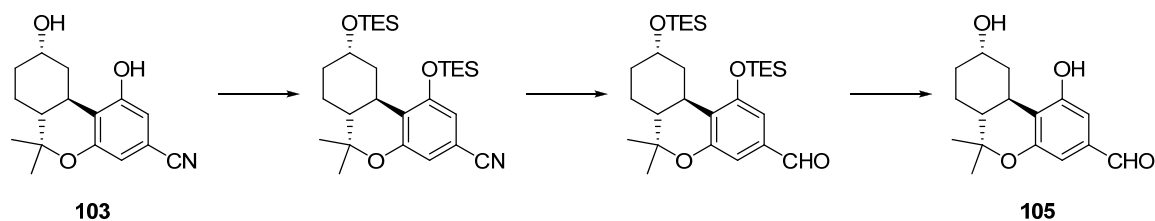
$^{13}\text{C}$  NMR ( $\text{MeOH}-d_4$ , 75 MHz):  $\delta$  193.9, 158.7, 157.0, 137.4, 120.8, 112.5, 107.2, 78.4, 71.2, 49.9, 39.3, 36.5, 35.5, 28.1, 27.1, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3338(br), 2976, 2934, 2872, 1716, 1684, 1577, 1558, 1338, 1144, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{16}\text{H}_{20}\text{O}_4$ : 276.1362, found: 276.1375 (4.8 ppm error)

EI+( $m/z$ ): 276 ( $\text{M}^+$ , 75), 258 (42), 243 (33), 215 (100), 189 (54), 142 (66)

$[\alpha]_{\text{D}}^{23}$  -154 ( $c$  0.007, MeOH)



Aldehyde **105** was prepared from **103** (55 mg, 0.20 mmol) in 61% yield over 3 steps (34 mg) as a colorless oil.

$^1\text{H}$  NMR (MeOH-  $d_4$ , 300 MHz):  $\delta$  9.72 (d,  $J$  = 0.9 Hz, 1H), 6.79 (s, 1H), 6.76 (s, 1H), 4.14 (br s, 1H), 3.46-3.39 (m, 1H), 3.02 (td,  $J$  = 11.0 Hz, 2.5 Hz, 1H), 1.97-1.90 (m, 1H), 1.71-1.46 (m, 4H), 1.38 (s, 3H), 1.24-1.13 (m, 1H), 1.09 (s, 3H)

$^{13}\text{C}$  NMR (MeOH-  $d_4$ , 75 MHz):  $\delta$  194.0, 158.8, 157.2, 137.3, 121.7, 112.5, 107.2, 78.3, 67.4, 50.4, 37.1, 34.1, 31.1, 27.9, 23.7, 19.3

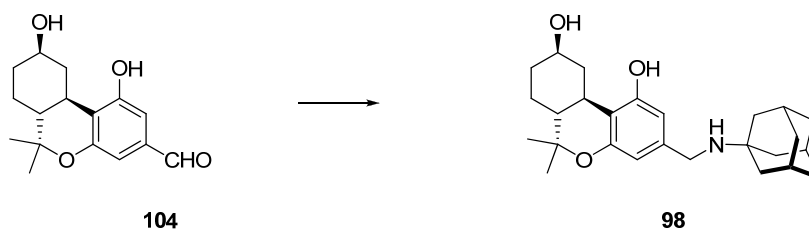
IR (thin film,  $\text{cm}^{-1}$ ): 3373(br), 2979, 2940, 2874, 1684, 1576, 1334, 1138, 1046

HR EI+ Mass Spec. Calculated for  $\text{C}_{16}\text{H}_{20}\text{O}_4$ : 276.1362, found: 276.1357 (1.6 ppm error)

EI+ ( $m/z$ ): 276 ( $\text{M}^+$ , 23), 258 (62), 215 (100), 207 (32)

$[\alpha]_{\text{D}}^{23}$  -144 ( $c$  0.008, MeOH)





### General Procedure for Reductive Amination

To a round bottom flask equipped with a stir bar, reflux condenser and Dean-Stark trap was added aldehyde **104** (10 mg, 0.036 mmol), 1-adamantanamine (6 mg, 0.040 mmol) and two 4Å molecular sieve beads in benzene. The reaction mixture was heated at reflux overnight. The progress of the reaction was followed by IR, monitoring the disappearance of the carbonyl absorption. The solvent was removed under vacuum and the crude imine was dissolved in dry MeOH and was treated with a spatula tip of 10% Pd/C. The reaction flask was purged with H<sub>2</sub> gas three times and the mixture was allowed to stir at room temperature overnight. The Pd/C was filtered off through a plug of Celite. The crude product was purified on silica gel using 2.5, 5, 10% MeOH/ CH<sub>2</sub>Cl<sub>2</sub> as the eluent resulting in amine **98** as a brown oil (12 mg, 81% yield over the 2 steps).

HPLC (0.10 cm x 25 cm Luna C8(2) 5 $\mu$ , 20 - 60% MeCN in water (both containing 0.1% HCO<sub>2</sub>H) over 30 min, 3 mL/min, UV detection at 280 nm) 15.87 min and 96.1% chemical purity.

<sup>1</sup>H NMR (MeOH- *d*<sub>4</sub>, 500 MHz):  $\delta$  6.26 (d, *J* = 1.0 Hz, 1H), 6.24 (d, *J* = 1.0 Hz, 1H), 3.74 (m, 1H), 3.52 (br s, 3H), 2.44 (td, *J* = 11.2 Hz, 2.3 Hz, 1H), 2.14-2.06 (m, 4H), 1.90 (m, 1H), 1.81-1.63 (m, 13H), 1.47-1.29 (s, 5H), 1.19 (td, *J* = 12.8 Hz, 3.3 Hz, 1H), 1.01 (s, 3H), 0.92 (m, 1H)

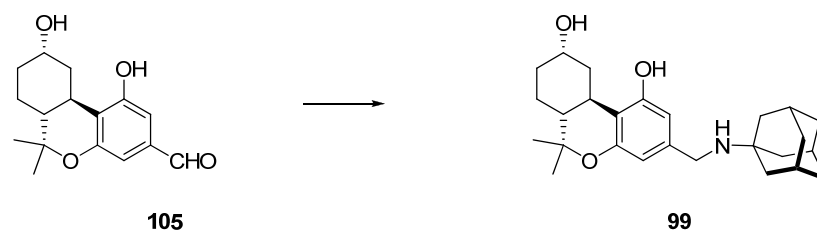
<sup>13</sup>C NMR (MeOH- *d*<sub>4</sub>, 126 MHz):  $\delta$  158.1, 156.3, 140.8, 112.2, 109.8, 108.6, 77.7, 71.3, 52.4, 50.3, 45.3, 42.8, 40.0, 37.7, 36.7, 35.0, 31.0, 28.2, 27.2, 19.1

IR (thin film, cm<sup>-1</sup>): 3282(br), 2976, 2906, 2844, 1576, 1363, 1232, 1134, 1054

HR EI+ Mass Spec. Calculated for C<sub>26</sub>H<sub>37</sub>NO<sub>3</sub>: 411.2773, found: 411.2760 (3.3 ppm error)

EI+(*m/z*): 411 (M<sup>+</sup>, 10), 207 (23), 151 (82), 135 (28), 94 (100), 77 (30), 67 (23)

$[\alpha]_D^{23}$  -110 (*c* 0.008, MeOH)



Amine **99** was prepared from **105** (12 mg, 0.043 mmol) in 78% yield (14 mg) over 2 steps as a colorless oil.

Chiral HPLC (0.10 cm x 25 cm Luna C8(2) 5 $\mu$ , 20 - 60% MeCN in water (both containing 0.1% HCO<sub>2</sub>H) over 30 min, 3 mL/min, UV detection at 280 nm) 16.72 min and 98.5% chemical purity.

<sup>1</sup>H NMR (MeOH- *d*<sub>4</sub>, 500 MHz):  $\delta$  6.30 (d, *J* = 1.5 Hz, 1H), 6.28 (d, *J* = 1.5 Hz, 1H), 4.12 (m, 1H), 3.66 (s, 2H), 3.39 (m, 1H), 2.94 (td, *J* = 11.7 Hz, 2.3 Hz, 1H), 2.13 (br s, 3H), 1.93 (m, 1H), 1.85-1.81 (m, 6H), 1.78-1.59 (m, 8H), 1.56-1.42 (m, 2H), 1.35 (s, 3H), 1.14 (ddd, *J* = 14.0 Hz, 11.8 Hz, 2.3 Hz, 1H), 1.06 (s, 3H)

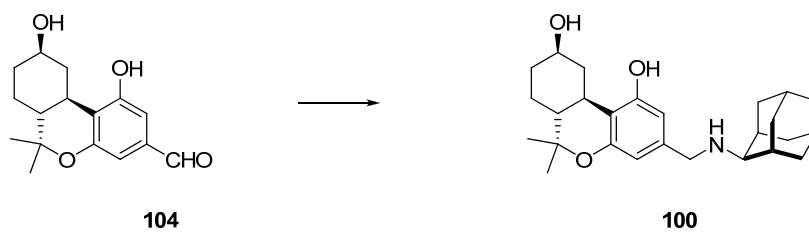
<sup>13</sup>C NMR (MeOH- *d*<sub>4</sub>, 126 MHz):  $\delta$  158.3, 156.8, 113.7, 110.3, 108.8, 77.8, 67.5, 50.8, 45.1, 41.6, 37.6, 37.3, 34.2, 30.9, 30.5, 28.0, 23.7, 19.3

IR (thin film, cm<sup>-1</sup>): 3276(br), 2975, 2911, 2850, 1621, 1578, 1451, 1429, 1134

HR EI+ Mass Spec. Calculated for C<sub>26</sub>H<sub>37</sub>NO<sub>3</sub>: 411.2773, found: 411.2791 (4.2 ppm error)

EI+(*m/z*): 411 (M<sup>+</sup>, 3), 151 (23), 97 (11), 95 (24), 94 (100), 83 (13), 81 (12), 71 (13), 69 (19)

[ $\alpha$ ]<sub>D</sub><sup>23</sup> -86 (*c* 0.0058, MeOH)



Amine **100** was prepared from **104** (10 mg, 0.036 mmol) in 60% yield (9 mg) over 2 steps as a colorless oil.

Chiral HPLC (0.10 cm x 25 cm Luna C8(2) 5 $\mu$ , 20 - 60% MeCN in water (both containing 0.1% HCO<sub>2</sub>H) over 30 min, 3 mL/min, UV detection at 280 nm) 16.47 min and 94.7% chemical purity.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz):  $\delta$  6.28 (d,  $J$  = 1.5 Hz, 1H), 6.24 (d,  $J$  = 1.5 Hz, 1H), 3.74 (m, 1H), 3.56 (br s, 2H), 3.54-3.50 (m, 1H), 2.77 (br s, 1H), 2.45 (td,  $J$  = 11.2 Hz, 2.3 Hz, 1H), 2.11 (m, 1H), 2.04-1.97 (m, 2H), 1.96-1.69 (m, 11H), 1.59-1.53 (m, 2H), 1.47-1.33 (m, 5H), 1.18 (m, 1H), 1.03 (s, 3H), 0.95 (m, 1H)

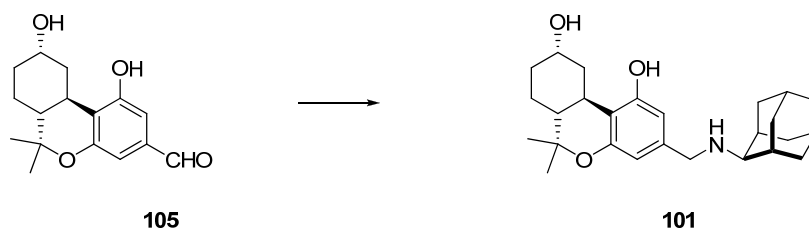
<sup>13</sup>C NMR (CDCl<sub>3</sub>, 126 MHz):  $\delta$  158.1, 156.3, 140.8, 112.2, 109.8, 108.6, 77.7, 71.3, 52.4, 50.3, 45.4, 42.8, 40.0, 37.7, 35.0, 31.0, 28.2, 27.2, 19.1

IR (thin film, cm<sup>-1</sup>): 23291(br), 2980, 2904, 2844, 1576, 1371, 1241, 1134, 1056

HR EI+ Mass Spec. Calculated for C<sub>26</sub>H<sub>37</sub>NO<sub>3</sub>: 411.2773, found: 411.2756 (4.2 ppm error)

EI+( $m/z$ ): 411 (M<sup>+</sup>, 17), 207 (19), 135 (21), 94 (100)

$[\alpha]_D^{23}$  -111 ( $c$  0.0094, MeOH)



Compound **101** was prepared from **105** (10 mg, 36  $\mu$ mol) in 84% yield (12.5 mg) over 2 steps as a colorless oil.

Chiral HPLC (0.10 cm x 25 cm Luna C8(2) 5 $\mu$ , 20 - 60% MeCN in water (both containing 0.1% HCO<sub>2</sub>H) over 30 min, 3 mL/min, UV detection at 280 nm) 17.09 min and 96.9% chemical purity.

<sup>1</sup>H NMR (MeOH- *d*<sub>4</sub>, 500 MHz):  $\delta$  6.37-6.35 (m, 2H), 4.14-4.11 (m, 1H), 3.89 (br s, 2H), 3.39(m, 1H), 3.16 (br s, 1H), 2.96 (td, *J* = 11.1 Hz, 2.5 Hz, 1H), 2.10 (br s, 2H), 2.00-1.87 (m, 7H), 1.82-1.73 (m, 4H), 1.71-1.60 (m, 4H), 1.57-1.44 (m, 2H), 1.36 (s, 3H), 1.16 (ddd, *J* = 14.0 Hz, 11.9 Hz, 2.2 Hz, 1H), 1.07 (s, 3H)

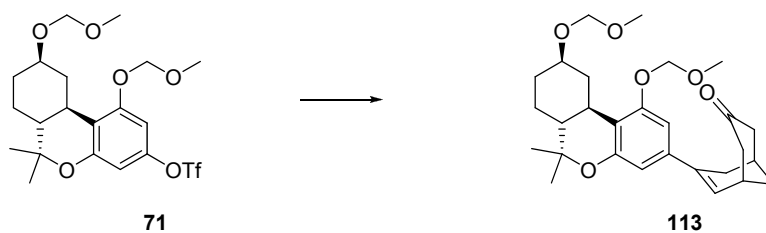
<sup>13</sup>C NMR (MeOH- *d*<sub>4</sub>, 126 MHz):  $\delta$  158.5, 157.1, 110.9, 109.2, 78.0, 67.5, 62.7, 50.7, 50.3, 38.3, 38.1, 37.5, 34.2, 31.5, 31.2, 30.5, 28.6, 28.4, 27.9, 23.7, 19.3

IR (thin film, cm<sup>-1</sup>): 3329(br), 2918, 1619, 1584, 1458, 1431, 1135

HR EI+ Mass Spec. Calculated for C<sub>26</sub>H<sub>37</sub>NO<sub>3</sub>: 411.2773, 411.2762 (2.7 ppm error)

EI+(*m/z*): 391 (M<sup>+</sup>, 9), 262 (24), 207 (19), 151 (17), 150 (100), 69 (15)

[ $\alpha$ ]<sub>D</sub><sup>23</sup> -84 (*c* 0.0056, MeOH)



A 4:1 solution of DMF/EtOH(abs.) over 4Å molecular sieves was degassed by bubbling Ar through the solution for 20 min. In a separate flask equipped with a stir bar was added triflate **71** (65 mg, 0.13 mmol), boronate **112** (45 mg, 0.17 mmol), K<sub>2</sub>CO<sub>3</sub> (62 mg, 0.45 mmol) and PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> (12 mg, 0.015 mmol). The reaction flask was evacuated and purged with Ar three times, then 2 mL of the DMF/EtOH mixture was added and the reaction mixture was heated at 70 °C for 6 h. The flask was cooled to room temperature; the mixture was filtered through Celite and concentrated directly onto Celite. The crude product was purified *via* flash column chromatography on silica gel eluting with 10, 20, 30 and 40% EtOAc/hexanes resulting in ketone **113** as a clear, colorless oil as a mixture of diastereomers (55 mg, 87% yield).

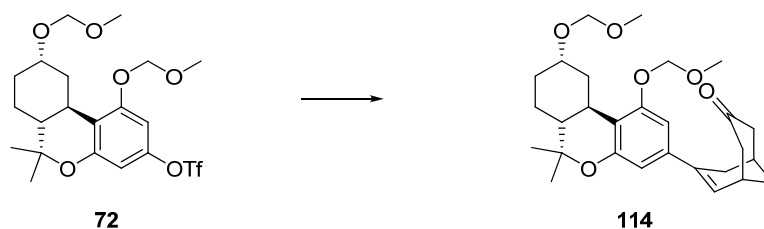


$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.63 (d,  $J = 6.0$  Hz, 1H), 6.51-6.47 (m, 1H), 6.12 (d,  $J = 5.7$  Hz, 1H), 5.22-5.12 (m, 2H), 4.73 (dd,  $J = 10.5$  Hz, 6.9 Hz, 1H), 3.74 (m, 1H), 3.49 (s, 3H), 3.43-3.34 (m, 4H), 2.87 (br s, 1H), 2.80-1.84 (m, 13H), 1.55-1.25 (m, 5H), 1.20-1.03 (m, 5H)

IR (thin film,  $\text{cm}^{-1}$ ): 2924, 2853, 1712, 1608, 1564, 1422, 1367, 1209, 1141, 1105, 1056, 1041

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{38}\text{O}_6$ : 470.2668, found: 470.2667 (0.3 ppm error)

EI+ ( $m/z$ ): 470 ( $\text{M}^+$ , 26), 85 (100), 83 (51), 69 (26), 67 (21)



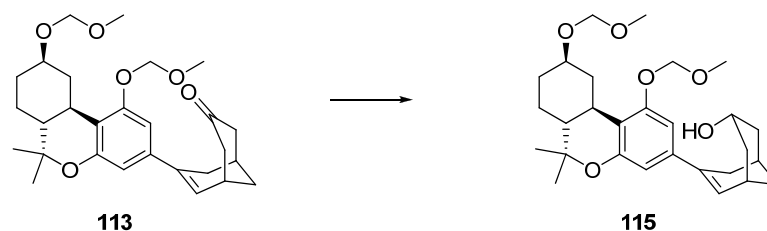
Compound **114** was prepared from **72** (65 mg, 0.13 mmol) in 67% yield (42 mg) as a colorless oil and a mixture of diastereomers.

$^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 300 MHz):  $\delta$  6.90-6.84 (m, 2H), 6.02 (m, 1H), 4.99-4.83 (m, 3H), 4.67 (d,  $J = 6.6$  Hz, 1H), 3.96 (br s, 1H), 3.51 (m, 1H), 3.32 (s, 3H), 3.21-3.12 (m, 4H), 2.43 (m, 1H), 2.30-1.89 (m, 8H), 1.58-1.25 (m, 8H), 1.18-1.04 (m, 5H)

IR (thin film,  $\text{cm}^{-1}$ ): 2972, 2931, 2813, 1712, 1610, 1563, 1153, 1049, 921

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{38}\text{O}_6$ : 470.2668, found: 470.2679 (2.3 ppm error)

EI+ ( $m/z$ ): 470 ( $\text{M}^+$ , 12), 408 (23), 376 (47), 364(69), 363(34), 361(11), 321(20), 307(15), 295(18), 220(21), 205(100), 69(78)



Ketone **113** (55 mg, 0.117 mmol) in 2 mL of MeOH was cooled to 0 °C and NaBH<sub>4</sub> (22 mg, 0.58 mmol) was added all at once and stirred for 30 min. The reaction was quenched with brine and the crude product was extracted with EtOAc and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was quickly purified *via* flash column chromatography eluting with 50% EtOAc/hexanes affording a diastereomeric mixture of endo-alcohol **115** as a clear, colorless oil (50 mg, 90% yield).

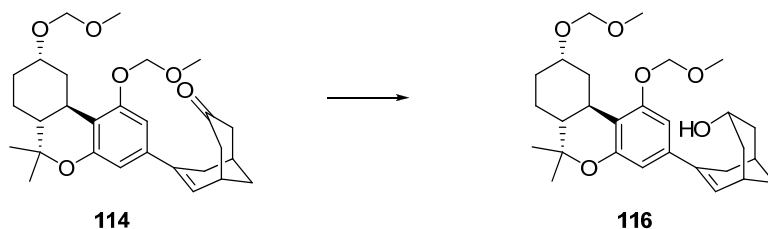
<sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 300 MHz): δ 6.99-6.95 (m, 2H), 6.43 (d, *J* = 6.0 Hz, 1H), 5.02 (m, 1H), 4.92-4.90 (d, *J* = 6.6 Hz, 1H), 4.77-4.70 (dd, *J* = 14.6 Hz, 6.8 Hz, 2H), 3.93 (br s, 1H), 3.74-3.67 (m, 2H), 3.28-3.23 (m, 7H), 2.60-2.48 (m, 4H), 2.20-1.81 (m, 5H), 1.68 (dt, *J* = 14.7 Hz, *J* = 5.1 Hz, 1H), 1.57-1.22 (m, 8H), 0.96 (s, 3H), 0.75 (m, 1H)

IR (thin film, cm<sup>-1</sup>): 3566(br), 2974, 2923, 2825, 1610, 1561, 1153, 1106, 1055, 1042

HR EI+ Mass Spec. Calculated for C<sub>28</sub>H<sub>40</sub>O<sub>6</sub>: 472.2825, found: 472.2823 (0.4 ppm error)

EI+(*m/z*): 472 (M<sup>+</sup>, 100), 366 (94), 360 (14), 279 (14), 149 (44), 91 (31), 79 (30), 69

(35)



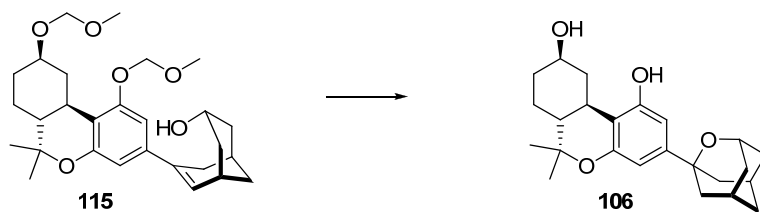
Alcohol **116** was prepared from **114** (34 mg, 0.072 mmol) in 82% yield (28 mg) as a colorless oil and a mixture of diastereomers.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.779 (m, 1H), 6.57-6.53 (m, 2H), 5.23-5.14 (m, 2H), 4.84 (d,  $J = 6.8$  Hz, 1H), 4.72 (d,  $J = 6.8$  Hz, 1H), 4.02 (br s, 1H), 3.95 (br s, 1H), 3.49 (s, 3H), 3.44 (s, 3H), 3.31 (m, 1H), 2.88 (app t,  $J = 10.4$  Hz, 1H), 2.81-2.50 (m, 2H), 2.38 (br s, 1H), 2.05-1.96 (m, 4H), 1.83-1.45 (m, 8H), 1.38 (s, 3H), 1.28-1.08 (m, 4H)

IR (thin film,  $\text{cm}^{-1}$ ): 3566(br), 2982, 2923, 2822, 2786, 1610, 1559, 1363, 1155, 1046, 921

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{40}\text{O}_6$ : 472.2825, found: 472.2816 (1.8 ppm error)

EI+ ( $m/z$ ): 472 ( $\text{M}^+$ , 62), 366 (100), 348 (32), 246 (41), 200 (21), 121 (25), 120 (23), 105 (82), 91 (29), 77 (45), 69 (92), 67 (30)



To alcohol **115** (26 mg, 0.055 mmol) in 2 mL of CH<sub>2</sub>Cl<sub>2</sub> was added *n*-BuSH (135 μL, 1.27 mmol) at rt followed by ZnBr<sub>2</sub> (62 mg, 0.28 mmol) all at once. The reaction mixture was stirred for 20 min and then diluted with EtOAc and saturated NaHCO<sub>3</sub>. The organic layer was washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified *via* flash column chromatography eluting with 40% then 50% EtOAc/hexanes affording oxaadamantane **106** (20 mg, 95% yield) as a white glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 7.50 min and 98.1% chemical purity.

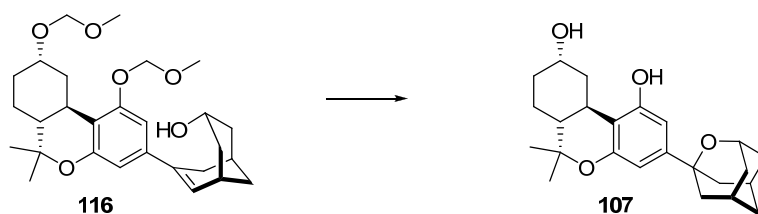
$^1\text{H}$  NMR ( $\text{C}_6\text{D}_6$ , 500 MHz):  $\delta$  8.51 (br s, 1H, OH), 6.87 (s, 1H), 6.79 (s, 1H), 4.24 (br s, 1H), 4.00 (m, 1H), 3.83 (m, 1H), 2.56 (br t,  $J = 10.8$  Hz, 1H), 2.15-1.87 (m, 8H), 1.63-1.15 (m, 12H), 0.97 (s, 3H), 0.78 (m, 1H)

$^{13}\text{C}$  NMR ( $\text{C}_6\text{D}_6$ , 126 MHz):  $\delta$  156.8, 155.6, 147.6, 111.0, 105.8, 104.3, 76.6, 73.0, 71.6, 69.2, 48.5, 42.3, 41.9, 38.6, 35.8, 35.7, 35.2, 34.2, 28.0, 26.4, 19.3

IR (thin film,  $\text{cm}^{-1}$ ): 3336(br), 2975, 2928, 2852, 1622, 1577, 1418, 1051

HR ESI+ Mass Spec. Calculated for  $\text{C}_{24}\text{H}_{32}\text{O}_4 + \text{H}^+$ : 385.2380, found: 385.2379 (0.3 ppm error)

$[\alpha]_{\text{D}}^{23}$  -99 ( $c$  0.008, MeOH)



Oxaadamantane **107** was prepared from **116** (28 mg, 0.059 mmol) in 79% yield (18 mg) as a white glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 16.93 min and 98.6% chemical purity.

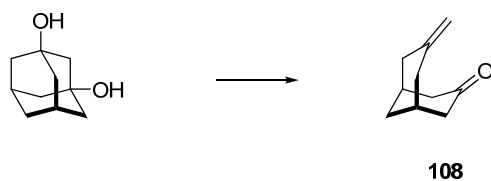
$^1\text{H}$  NMR (MeOH- $d_4$ , 300 MHz):  $\delta$  6.40 (d,  $J = 1.8$  Hz, 1H), 6.31 (d,  $J = 1.8$  Hz, 1H), 4.19-4.10 (m, 2H), 3.40 (m, 1H), 2.93 (td,  $J = 11.4$  Hz, 2.9 Hz, 1H), 2.21 (br s, 2H), 2.07-1.89 (m, 8H), 1.78-1.70 (m, 2H), 1.69-1.40 (m, 4H), 1.34 (s, 3H), 1.21-1.11 (m, 2H), 1.06 (s, 3H)

$^{13}\text{C}$  NMR (MeOH- $d_4$ , 75 MHz):  $\delta$  157.5, 156.1, 148.3, 112.4, 105.9, 104.5, 77.6, 73.9, 70.8, 67.6, 50.9, 43.0, 37.6, 36.5, 36.0, 34.2, 30.4, 29.0, 28.0, 23.7, 19.3

IR (thin film,  $\text{cm}^{-1}$ ): 3502(br), 2926, 2851, 1623, 1418, 1138

HR ESI+ Mass Spec. Calculated for  $\text{C}_{24}\text{H}_{32}\text{O}_4 + \text{H}^+$ : 385.2380, found: 385.2362 (4.7 ppm error)

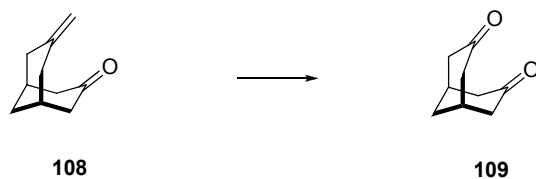
$[\alpha]_{\text{D}}^{23}$  -76 ( $c$  0.0088, MeOH)



To 1,3-adamantanediol (3.35 g, 19.9 mmol) in 80 mL of 1:1 pyridine/benzene was added benzenesulfonyl chloride (8.90 mL, 69.7 mmol) which was then heated to 75 °C overnight. The mixture was cooled to room temperature and solvent was removed under reduced pressure. The crude oil was then dissolved in EtOAc, washed with CuSO<sub>4</sub> and dried over MgSO<sub>4</sub>. The crude ketone **108** was then carried on to the next step. A pure sample could be obtained by flash column chromatography on silica gel eluting with 30-80% EtOAc/hexanes. Spectral data was identical to that reported in the literature.<sup>84</sup>

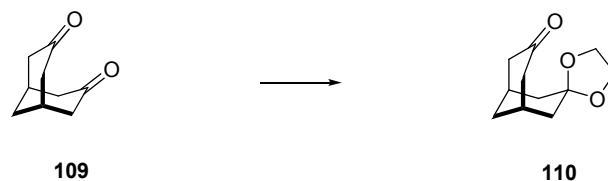
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz): δ 4.78 (s, 2H), 2.45-2.24 (m, 10H), 1.98-1.87 (m, 2H)



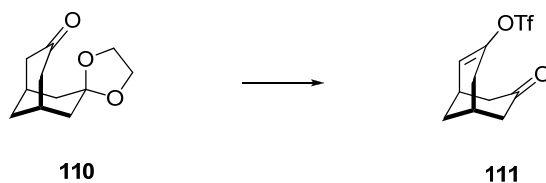


Crude ketone **108** was dissolved in 60 mL of  $\text{CH}_2\text{Cl}_2$  and ozone was bubbled through at  $-78^\circ\text{C}$  until the solution became blue in color. Oxygen was bubbled through for 15 min followed by  $\text{N}_2$  for an additional 15 min. Dimethylsulfide (10 eq) was then added and allowed to warm gradually to room temperature overnight. Solvent was removed under vacuum and the crude product was subjected to flash column chromatography on silica gel eluting with 50-80% EtOAc/hexanes affording **109** (2.00 g, 66% over 2 steps) as a white solid which was identical to the reported spectral data.<sup>84</sup>

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  2.85 (br s, 2H), 2.61-2.53 (m, 4H), 2.41-2.35 (m, 4H), 2.19 (br s, 2H)



To diketone **109** (1.70 g, 11.2 mmol) in 30 mL of benzene was added ethylene glycol (2.77 g, 44.7 mmol) and TsOH·H<sub>2</sub>O (212 mg, 1.12 mmol) at room temperature. The reaction flask was then equipped with a stir bar and Dean-Stark apparatus and heated to reflux for 6 h. The flask was cooled to room temperature, washed with water, saturated NaHCO<sub>3</sub>, brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was then subjected to flash column chromatography on silica gel eluting with 70% EtOAc/hexanes affording **110** (2.06 g, 94%) as a white solid with spectral data identical to that reported in the literature.<sup>84</sup>



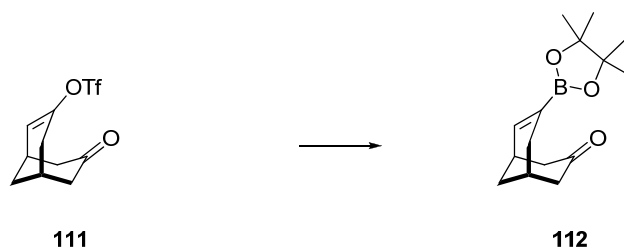
To a freshly prepared solution of LDA (made from diisopropylamine (540  $\mu$ L, 3.83 mmol) and *n*-BuLi in hexanes (1.37 mL, 3.57 mmol, 2.60 M) stirred at 0 °C for 30 min) in 10 mL of THF at -78 °C was added the ketone **110** (500 mg, 2.55 mmol) dropwise *via* cannula over 10 min. After 1.5 h at -78 °C PhNTf<sub>2</sub> (1.55 g, 4.33 mmol) in 5 mL of THF was added dropwise *via* cannula and gradually warmed to room temperature overnight. The reaction was quenched with saturated NaHCO<sub>3</sub>, diluted with Et<sub>2</sub>O, washed with brine and dried over MgSO<sub>4</sub>. The crude product was then passed through a plug of silica eluting with 50% EtOAc/hexanes. The crude triflate was then dissolved in 10mL of acetone and TsOH·H<sub>2</sub>O (49 mg, 0.26 mmol) was added at room temperature and stirred for 2 h. The reaction mixture was diluted with Et<sub>2</sub>O, washed with saturated NaHCO<sub>3</sub>, brine and dried over MgSO<sub>4</sub>. The crude triflate **111** was purified *via* flash column chromatography on silica gel eluting with 40-50% EtOAc/hexanes resulting in **111** as a white waxy solid (549 mg, 82% over 2 steps).

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  5.83 (d,  $J = 6.3$  Hz, 1H), 2.97 (br s, 1H), 2.78-2.71 (m, 2H), 2.62-2.37 (m, 4H), 2.24-1.98 (m, 3H)

IR (thin film,  $\text{cm}^{-1}$ ): 2937, 1716, 1685, 1417, 1211, 1141, 1069, 1035, 969

HR EI+ Mass Spec. Calculated for  $\text{C}_{10}\text{H}_{11}\text{F}_3\text{O}_4\text{S}$ : 284.0330, found: 284.0335 (1.6 ppm error)

EI+ ( $m/z$ ): 284 ( $\text{M}^+$ , 11), 227 (34), 151 (100), 93 (22), 81 (26), 77 (60), 68 (32)

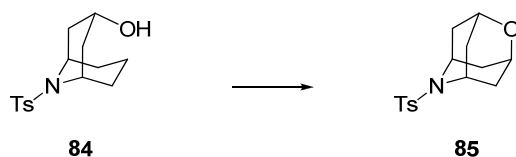


To the triflate **111** (130 mg, 0.457 mmol) in a round bottom flask charged with a stir bar was added flame dried  $\text{K}_2\text{CO}_3$  (95 mg, 0.69 mmol), bispinacolboronate (128 mg, 0.50 mmol),  $\text{PdCl}_2(\text{PPh}_3)_2$  (32 mg, 0.046 mmol) and  $\text{PPh}_3$  (24 mg, 0.092 mmol). The flask was then equipped with a reflux condenser and the system was evacuated and purged with Ar three times. Anhydrous and deoxygenated 1,4-dioxane (Ar bubbled through for 20 min) was then added and the reaction mixture was heated to  $70^\circ\text{C}$  for 7 h. The black reaction mixture was then cooled to rt, filtered through a pad of Celite and adsorbed onto Celite. The crude product was then purified *via* flash column chromatography on silica gel eluting with 20% EtOAc/hexanes affording **112** (87 mg, 73%) as a white waxy solid.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  6.54 (d,  $J = 5.1$  Hz, 1H), 2.74 (br s, 1H), 2.58-2.26 (m, 6H), 2.14-1.94 (m, 3H), 1.24 (s, 12H)

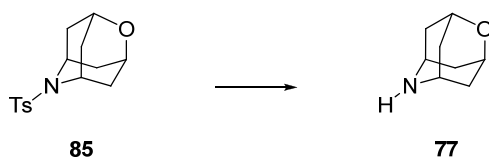
IR (thin film,  $\text{cm}^{-1}$ ): 2978, 2928, 1716, 1632, 1456, 1386, 1320, 1145

HR ESI+ Mass Spec. Calculated for  $\text{C}_{15}\text{H}_{23}\text{BO}_3 + \text{H}^+$ : 263.1813, found: 263.1809 (1.5 ppm error)



To a solution of powdered alcohol **84** (650 mg, 2.20 mmol) and finely powdered iodobenzene diacetate (1.10 g, 3.41 mmol) in 16.5 mL of cyclohexane under Ar was added I<sub>2</sub> (838 mg, 3.30 mmol) at room temperature. The mixture was stirred in a preheated oil bath set at 60 °C and irradiated (light source: slide projector ELMO omnigraphic 301AF, projection lamp: 120V-300W ANSI Code ELH; 3 cm from the flask and surrounded in Al foil to trap the light) for 1.5 h. The reaction was then quenched with 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, extracted with EtOAc, washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was then purified using flash column chromatography on silica gel eluting with 30% then 50% EtOAc/hexanes resulting in **85** (485 mg, 75%) as a white solid.

<sup>1</sup>H NMR NMR (300 MHz, CDCl<sub>3</sub>) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 4.29 (m, 2H), 4.08 (m, 2H), 2.41 (s, 3H), 1.93-1.99 (m, 4H), 1.70-1.75 (m, 4H)



Freshly washed Na (200 mg, 8.70 mmol) was added to naphthalene (1.33 g, 10.4 mmol) in 5 mL of DME under nitrogen at room temperature and stirred for 1.5 h resulting in a dark green solution. The green solution was then added dropwise via cannula to sulfonamide **85** (200 mg, 0.68 mmol) in 5 mL of DME at -50 °C until the dark green color persisted followed by an additional 15 min of stirring. The mixture was quenched with the dropwise addition of saturated NH<sub>4</sub>Cl solution until the green color dissipated. The reaction mixture was then diluted with Et<sub>2</sub>O, acidified to pH 1 with conc. HCl, organic layer separated, the aqueous layer was then basified with solid KOH until strongly basic, extracted with Et<sub>2</sub>O, washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude amine was then dissolved in hot hexanes and filtered using a Buchner funnel and concentrated resulting in amine **77** (80 mg, 85%) as a white solid. The TFA salt could be prepared from dissolving **77** in 1:1 CH<sub>2</sub>Cl<sub>2</sub>:TFA at 0 °C and then removing the solvent under vacuum resulting in a white solid which could be stored for months without any decomposition.

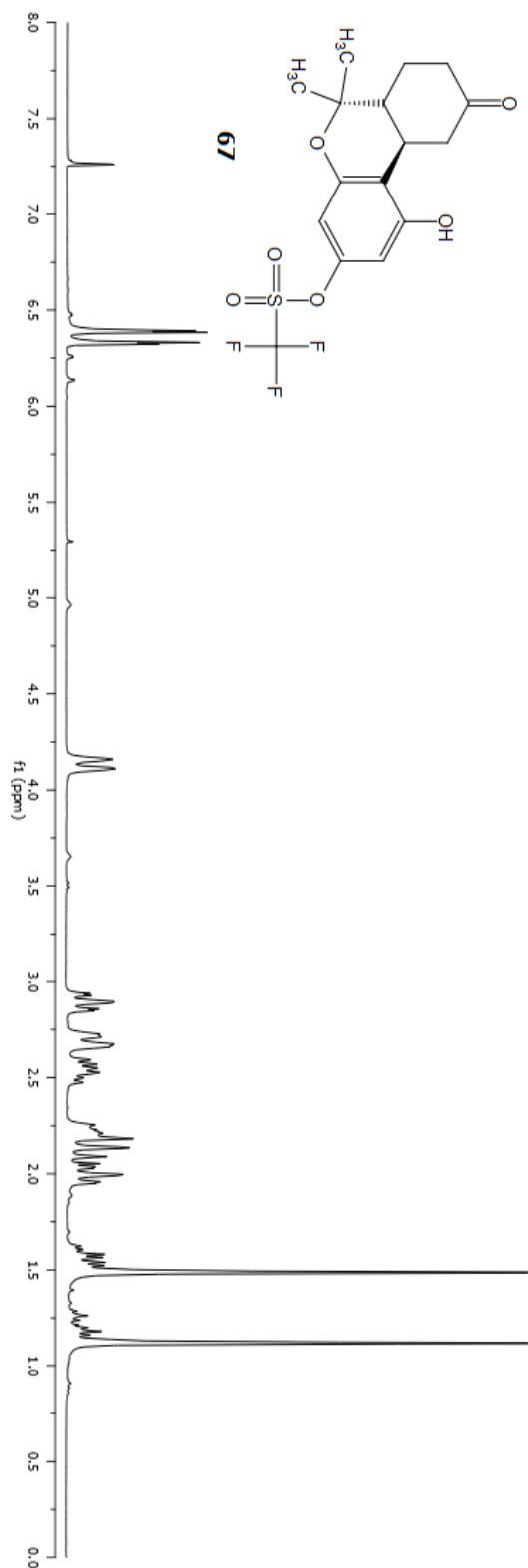
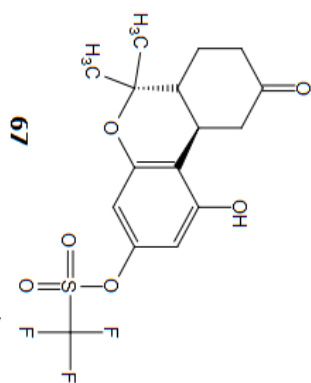
<sup>1</sup>H NMR (300 MHz, C<sub>6</sub>D<sub>6</sub>) δ 4.05 (m, 2H), 2.95 (m, 1H), 1.88-1.83 (m, 4H), 1.53-1.47 (m, 4H), 0.92 (br s, 1H)

<sup>13</sup>C NMR (75 MHz, C<sub>6</sub>D<sub>6</sub>) δ 67.3, 46.0, 36.6

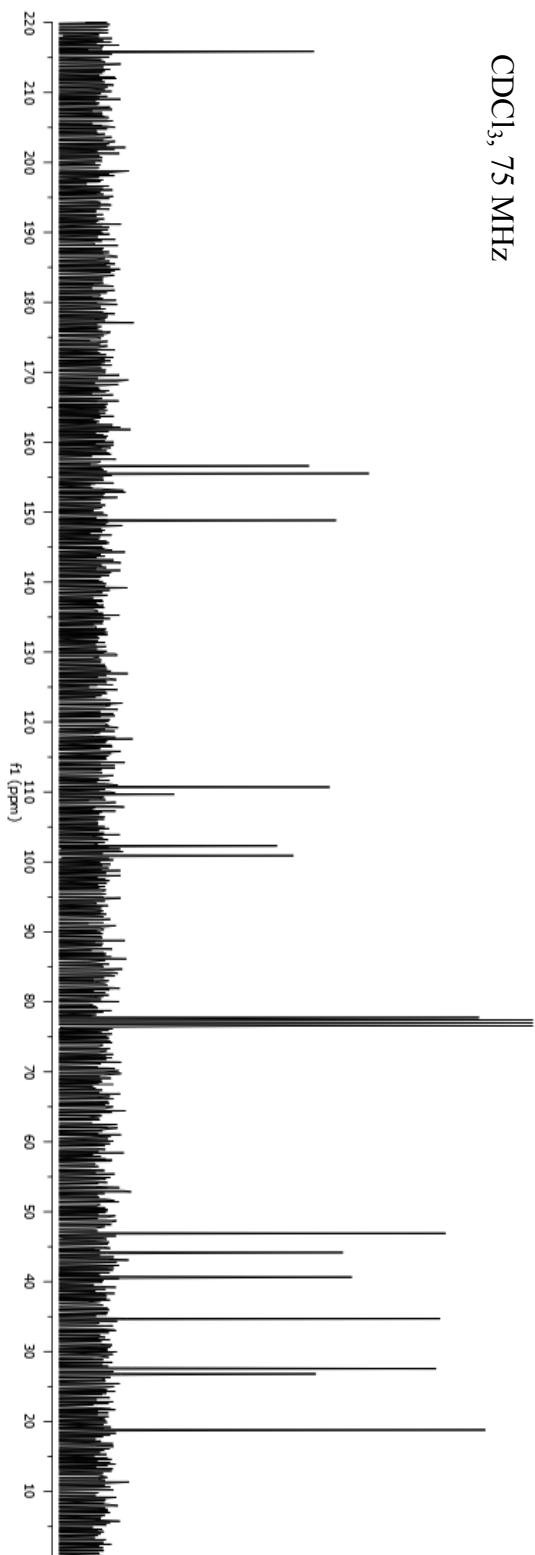
## **APPENDIX 1: SPECTRA FOR SELECTED COMPOUNDS IN PART I**



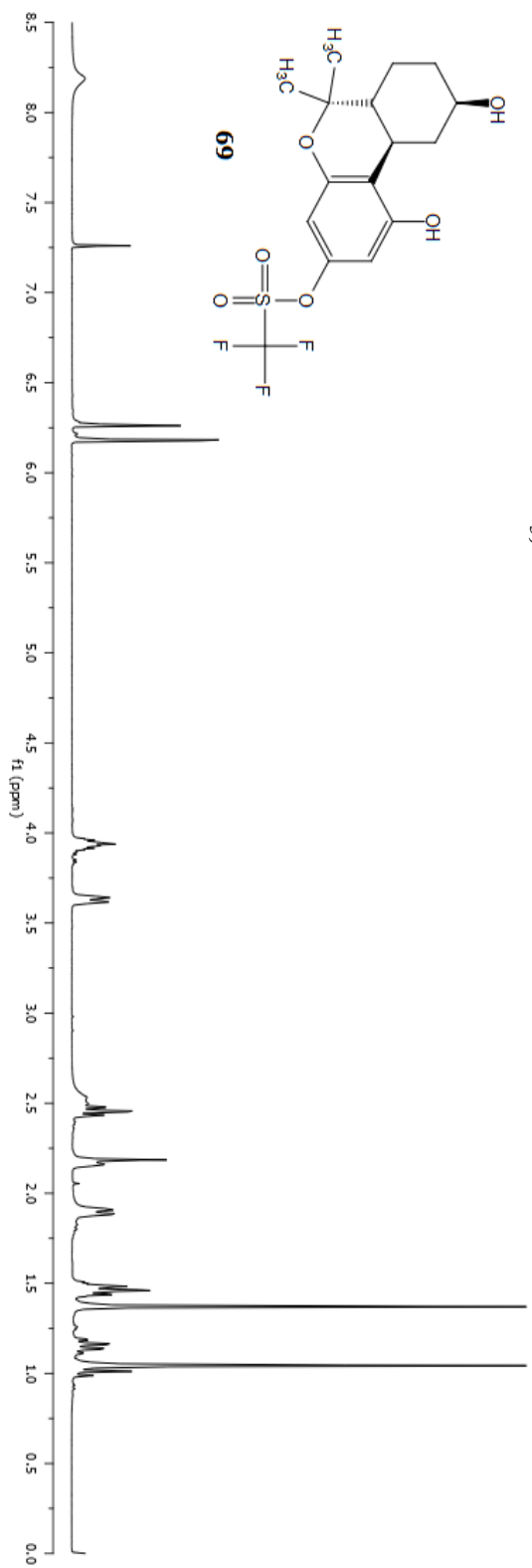
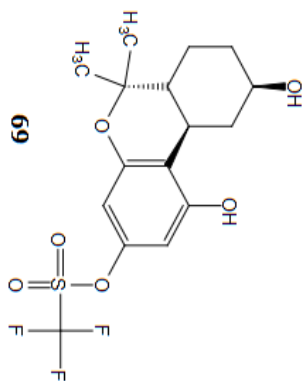
CDCl<sub>3</sub>, 300 MHz



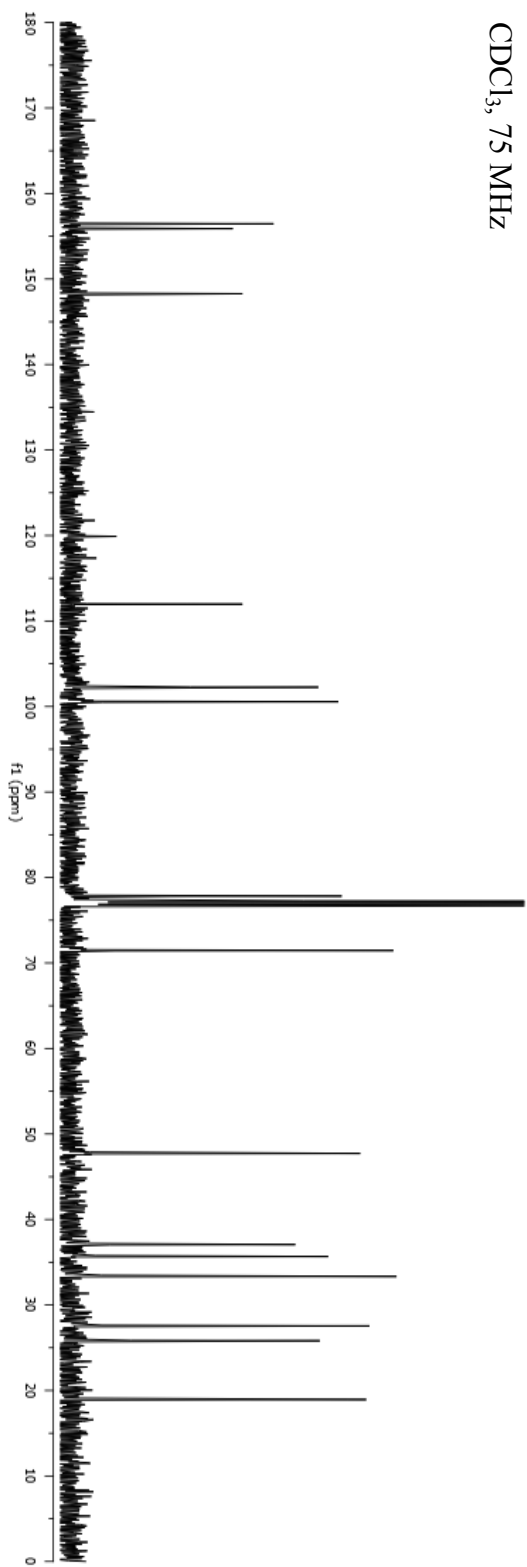
CDCl<sub>3</sub>, 75 MHz



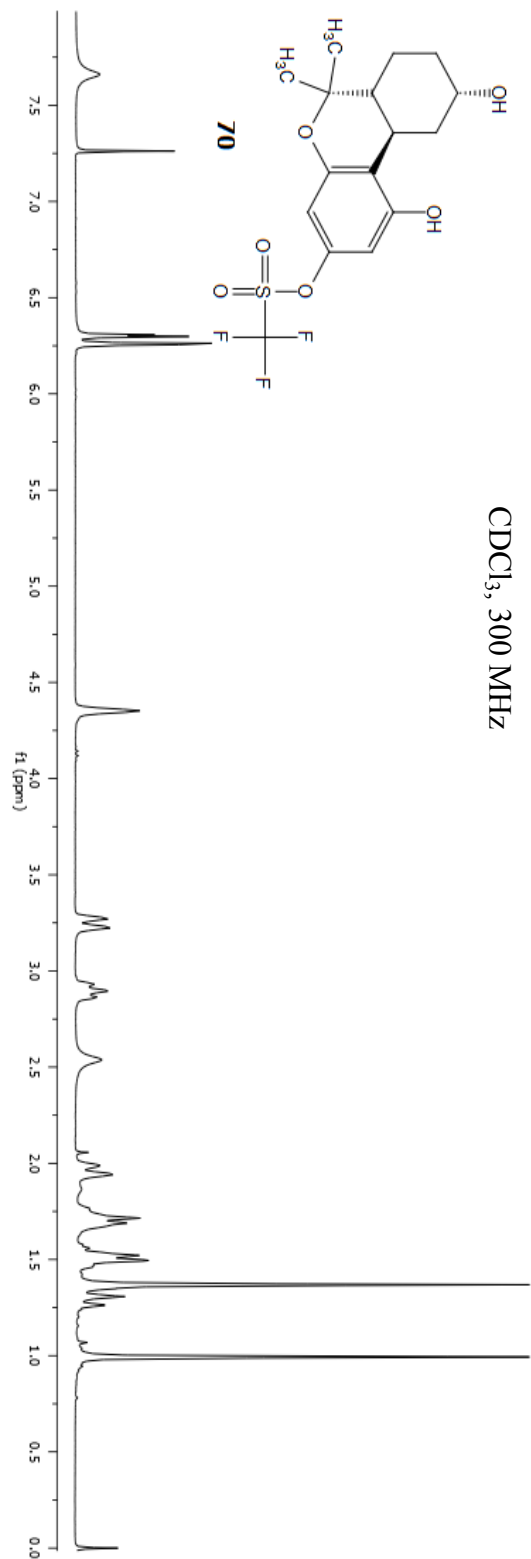
CDCl<sub>3</sub>, 300 MHz



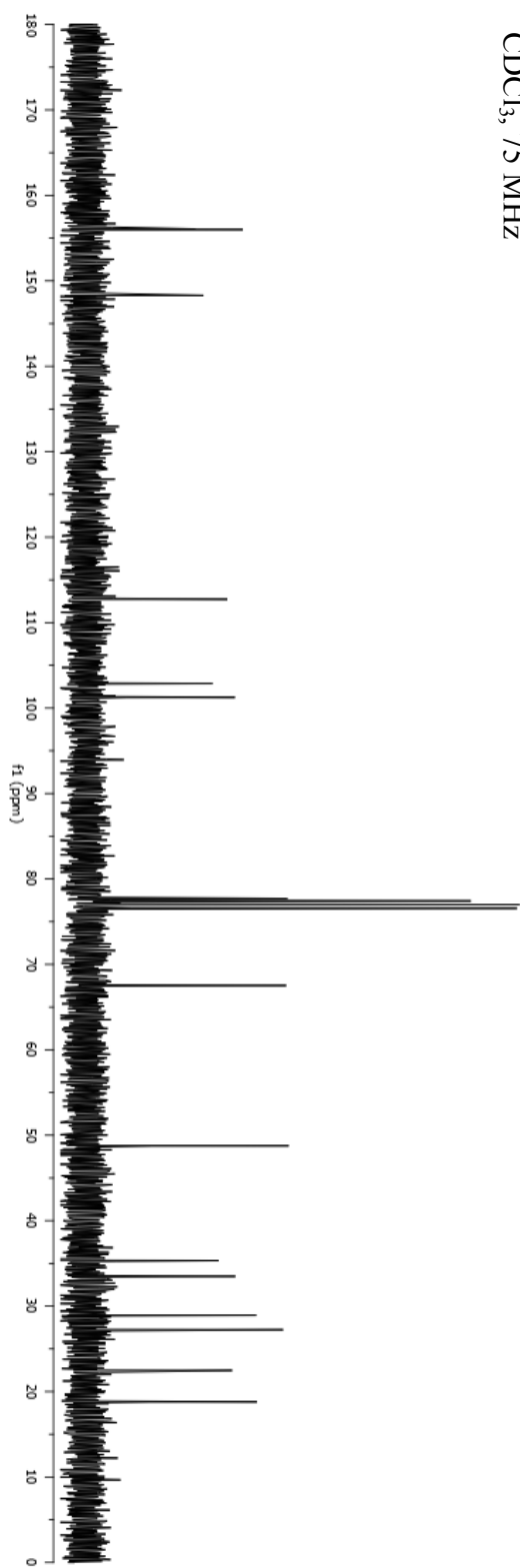
CDCl<sub>3</sub>, 75 MHz

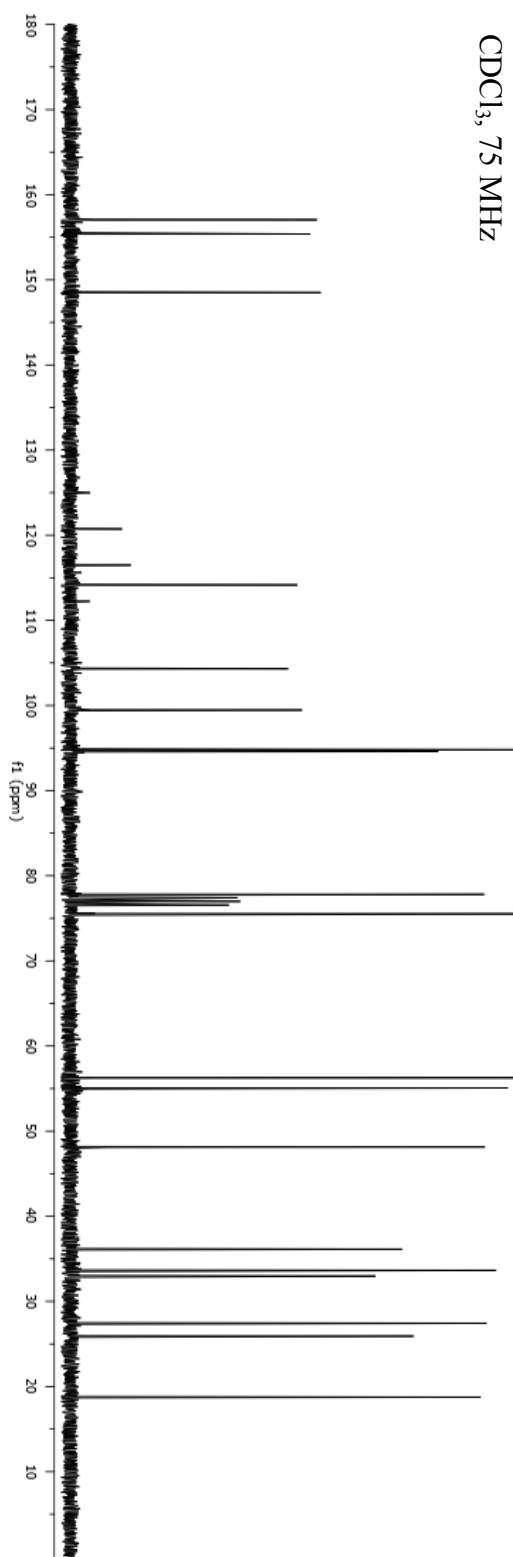
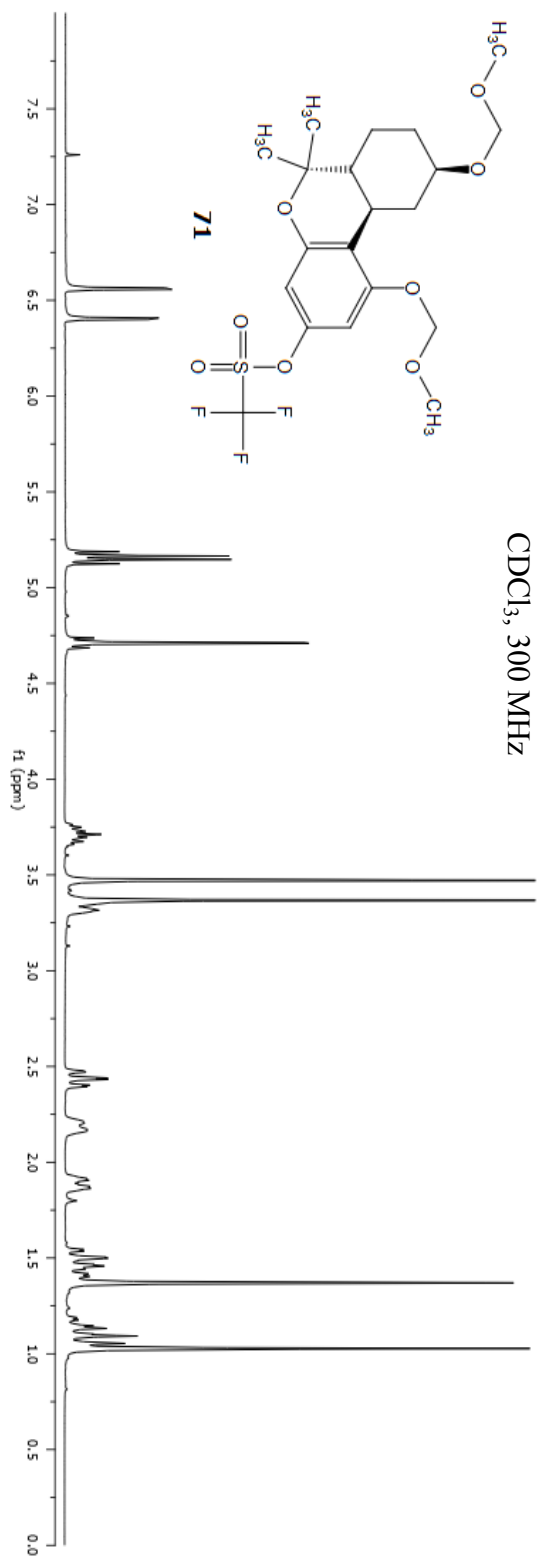


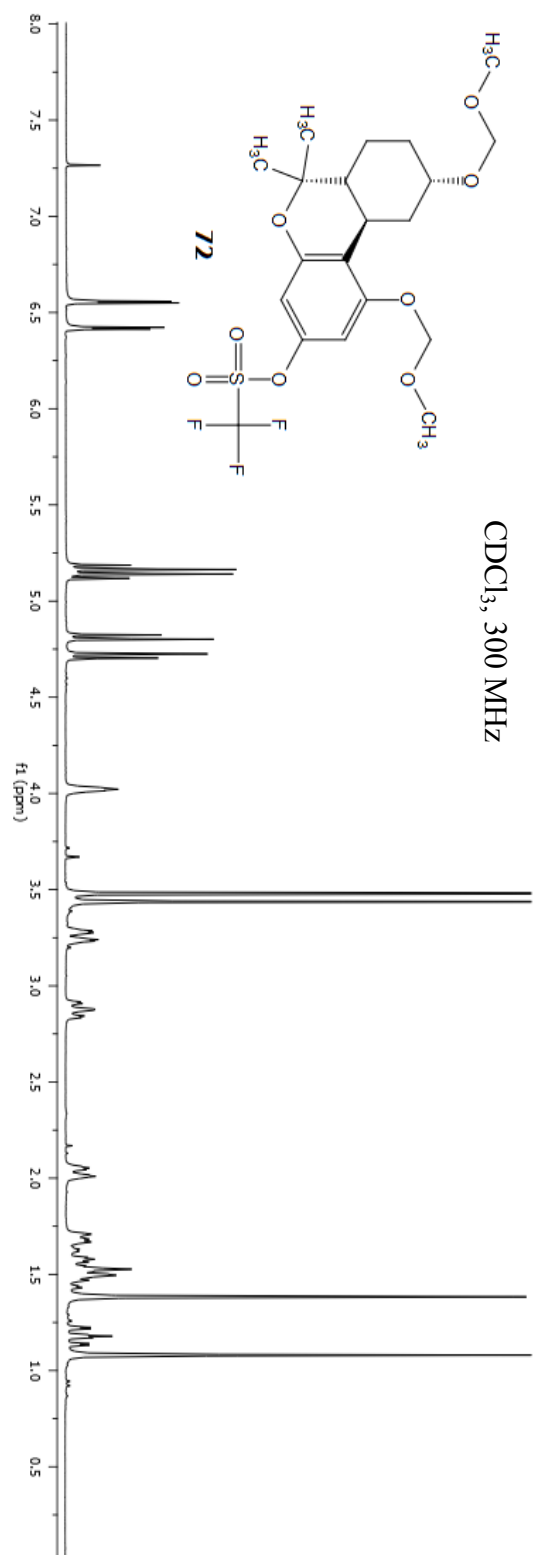
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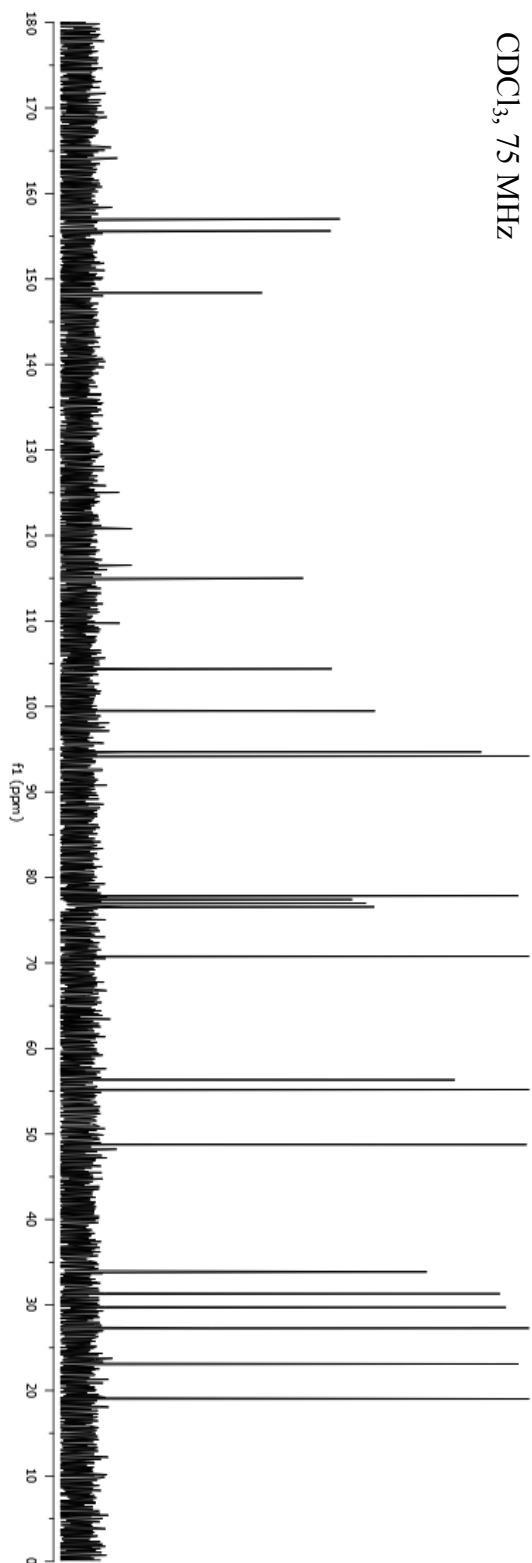
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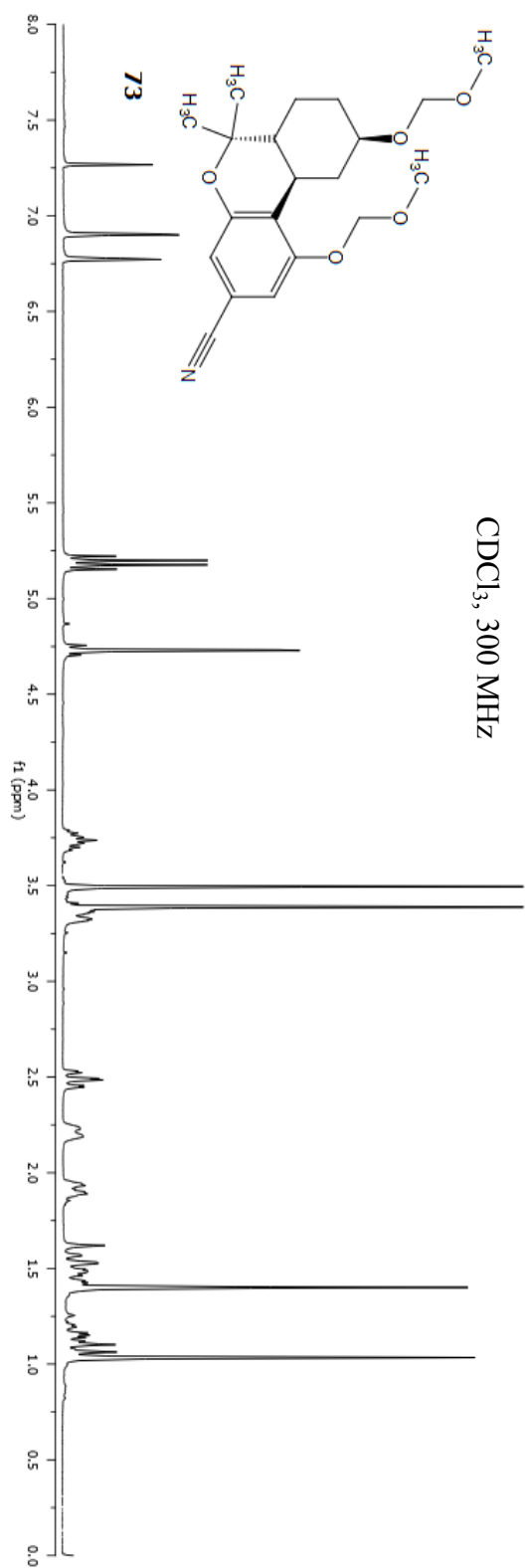
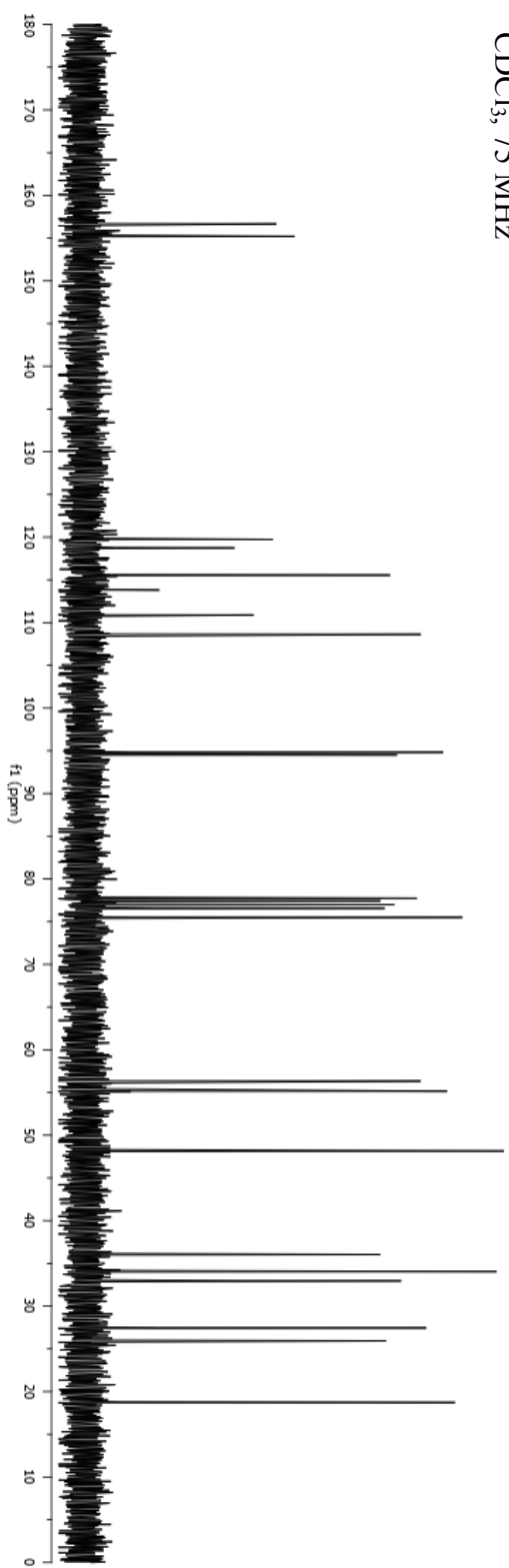


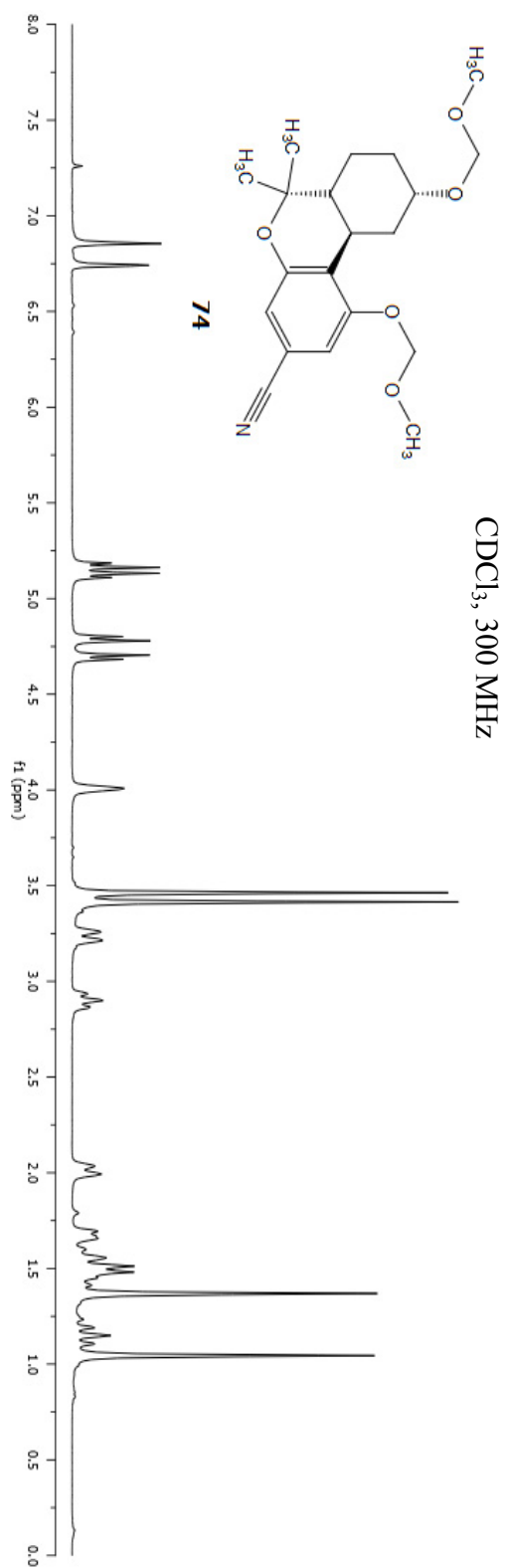




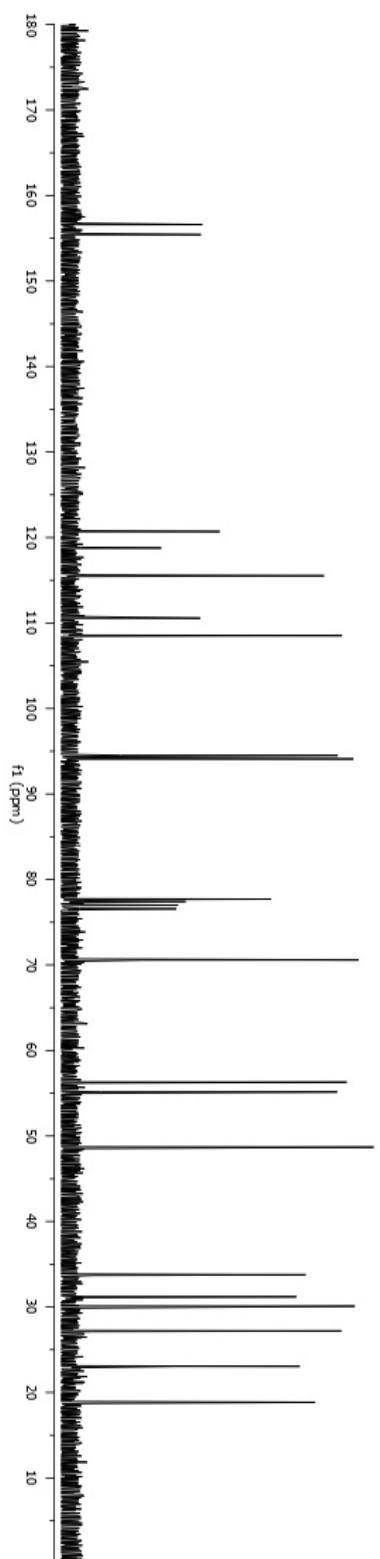
CDCl<sub>3</sub>, 75 MHz



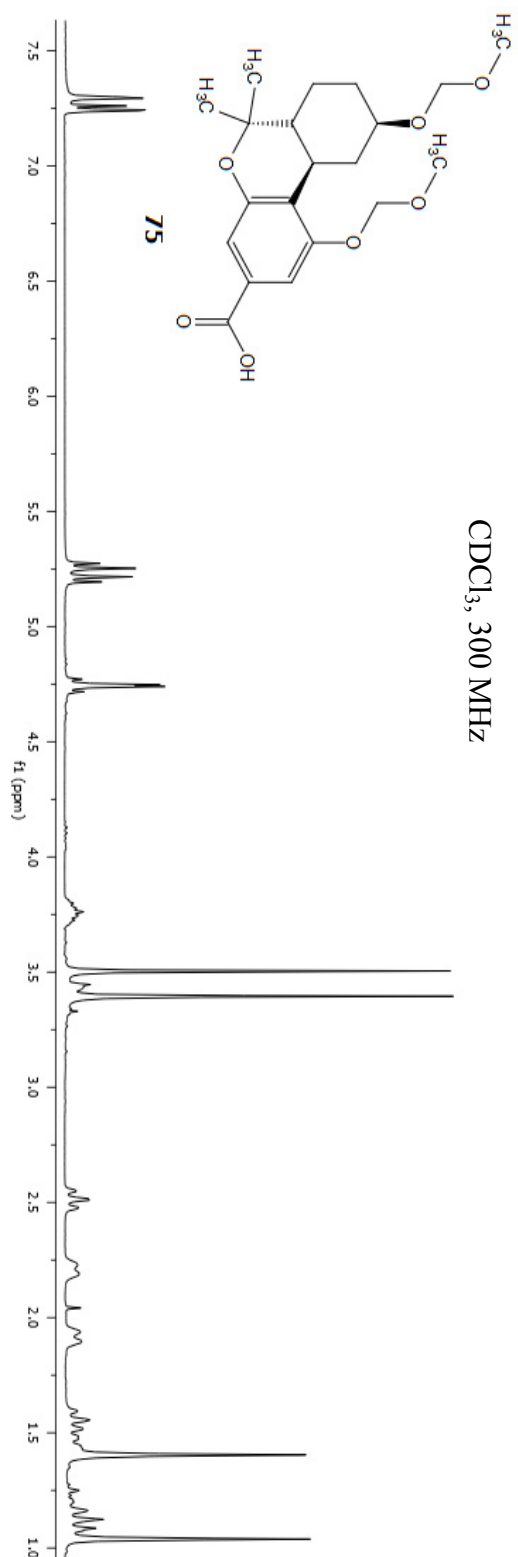
CDCl<sub>3</sub>, 75 MHz



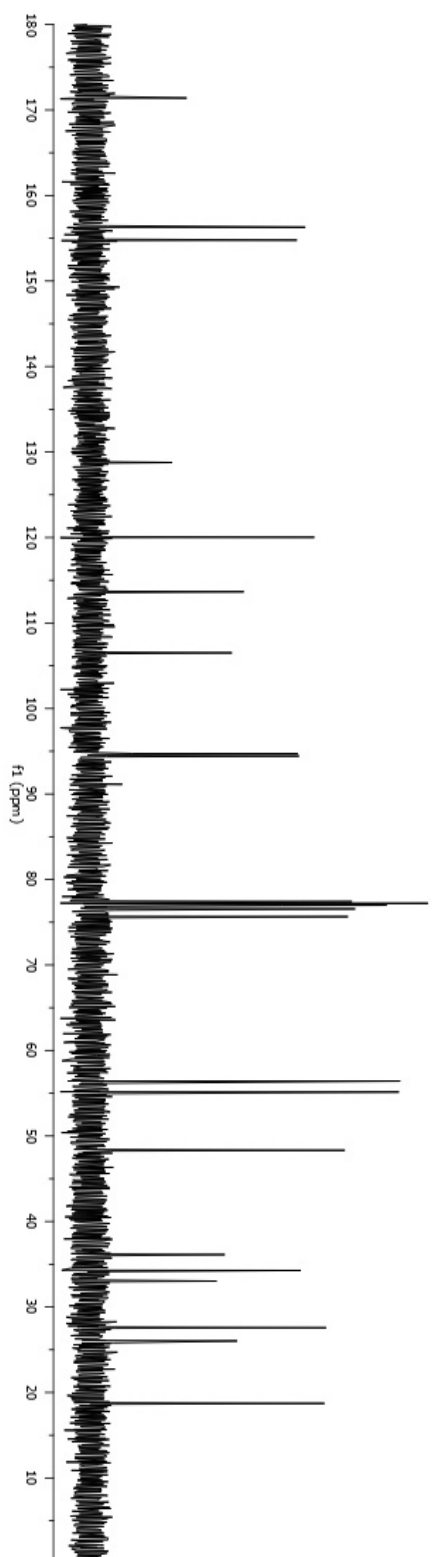
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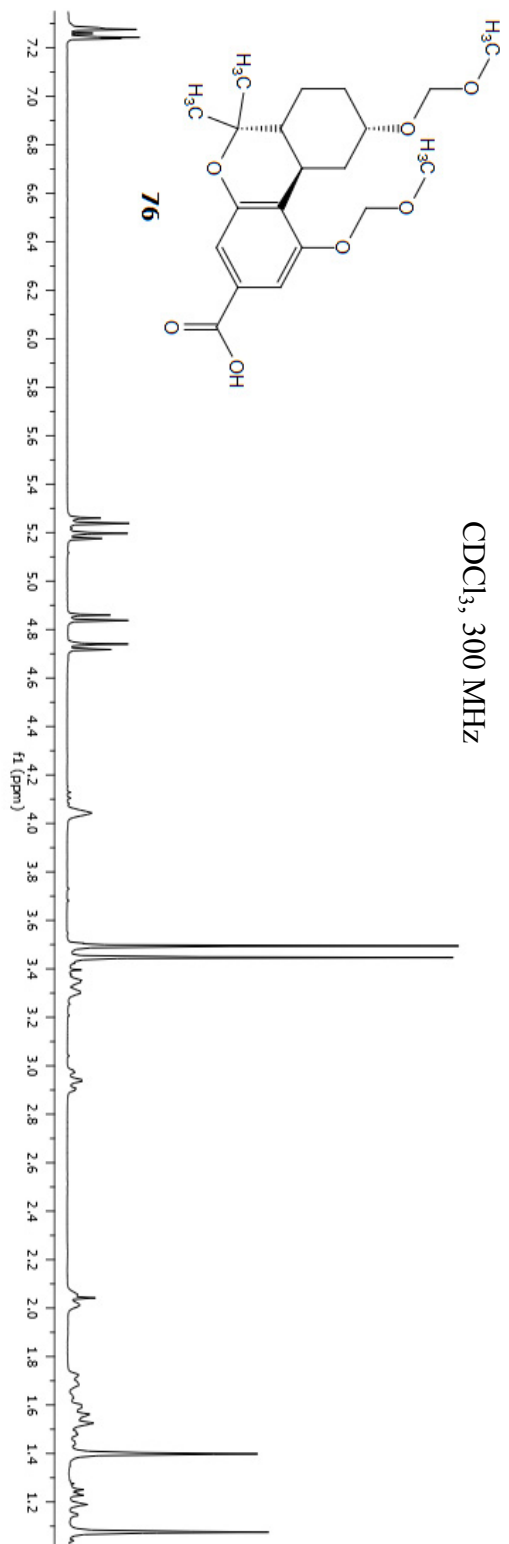
CDCl<sub>3</sub>, 300 MHz



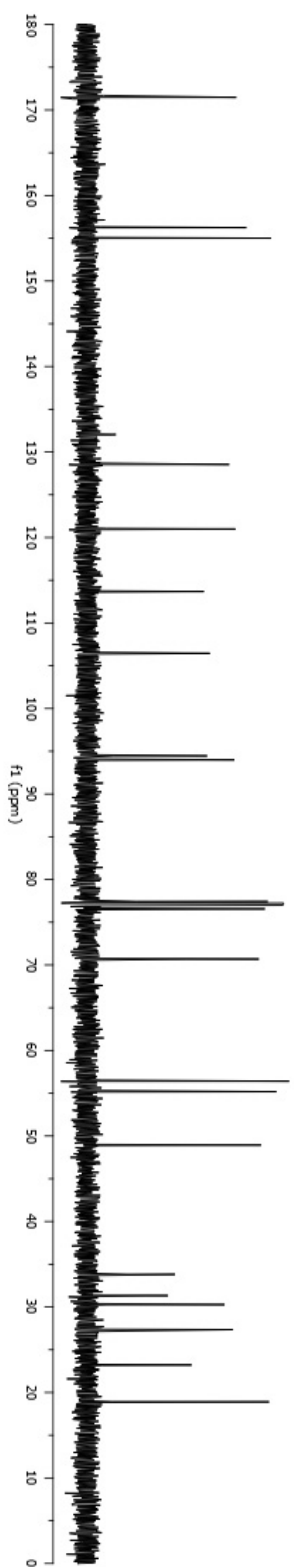
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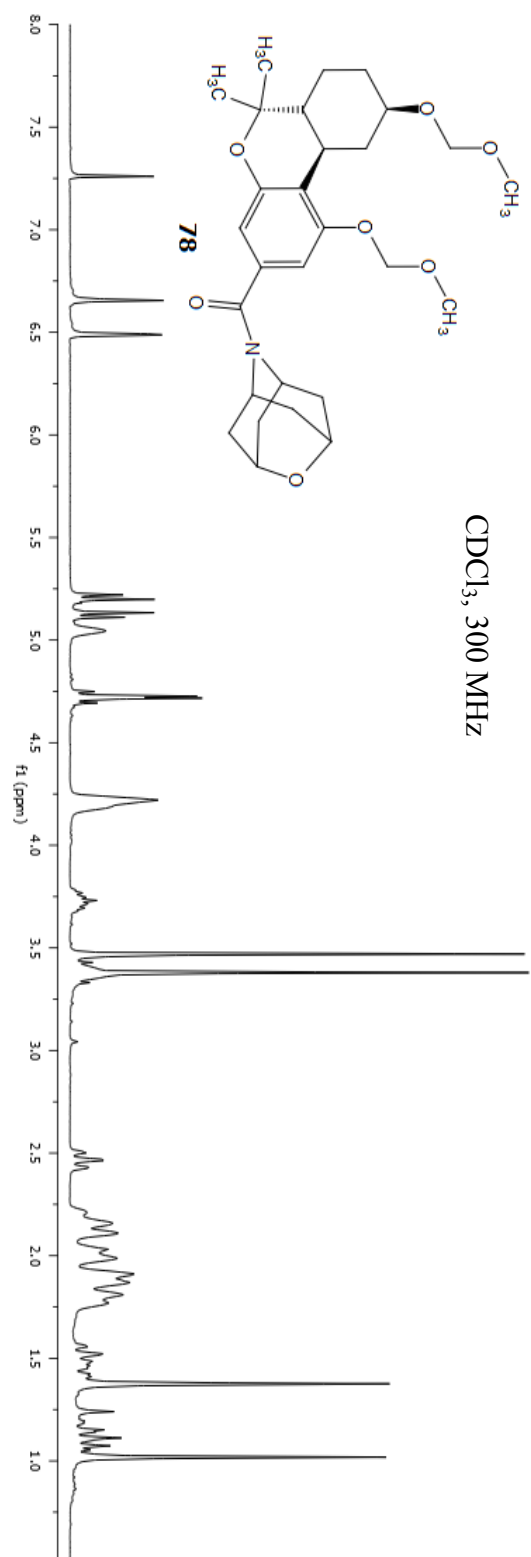




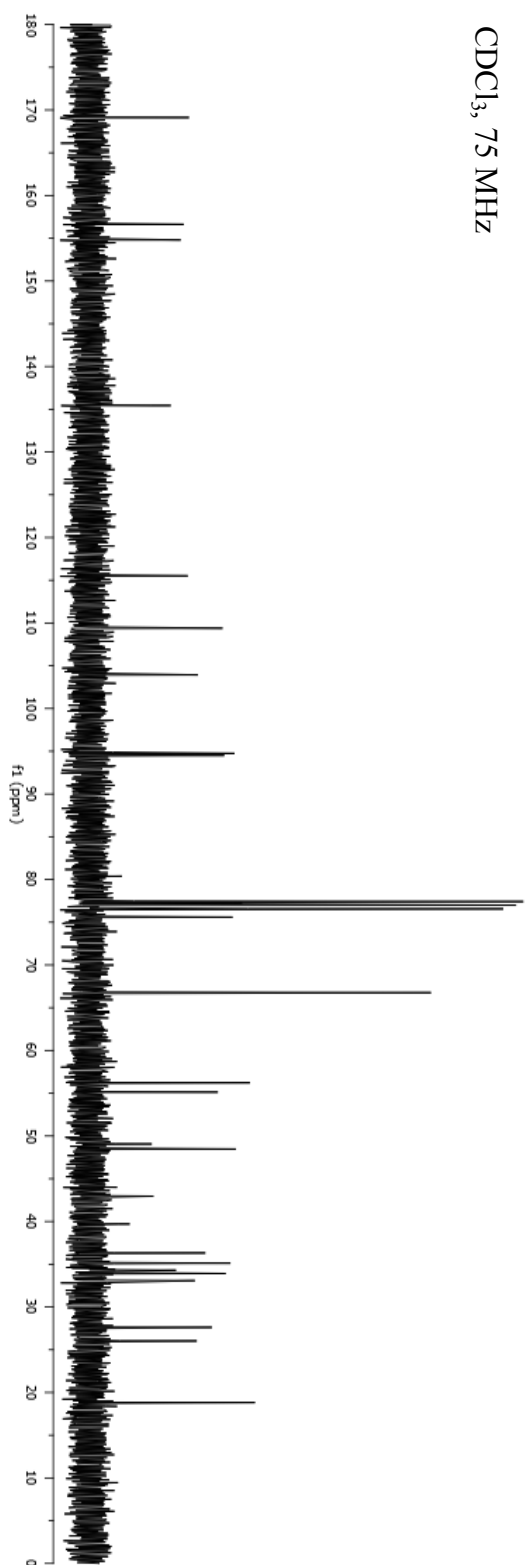


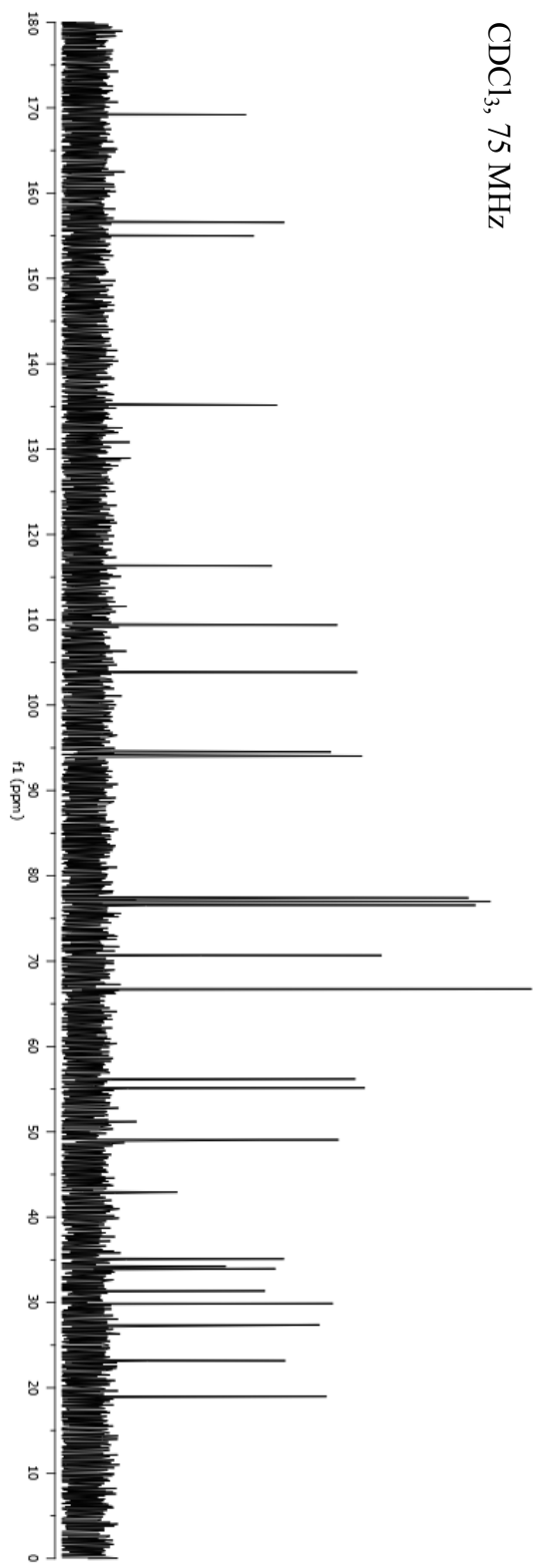
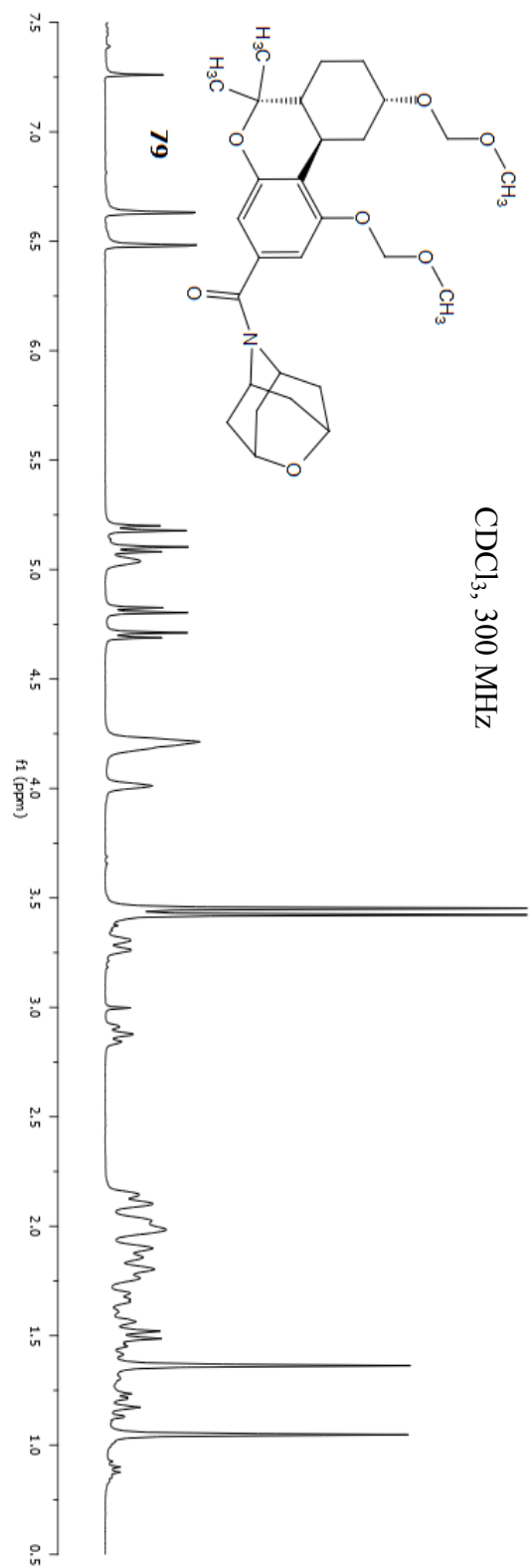
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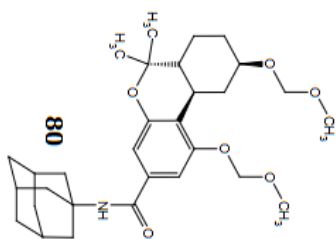
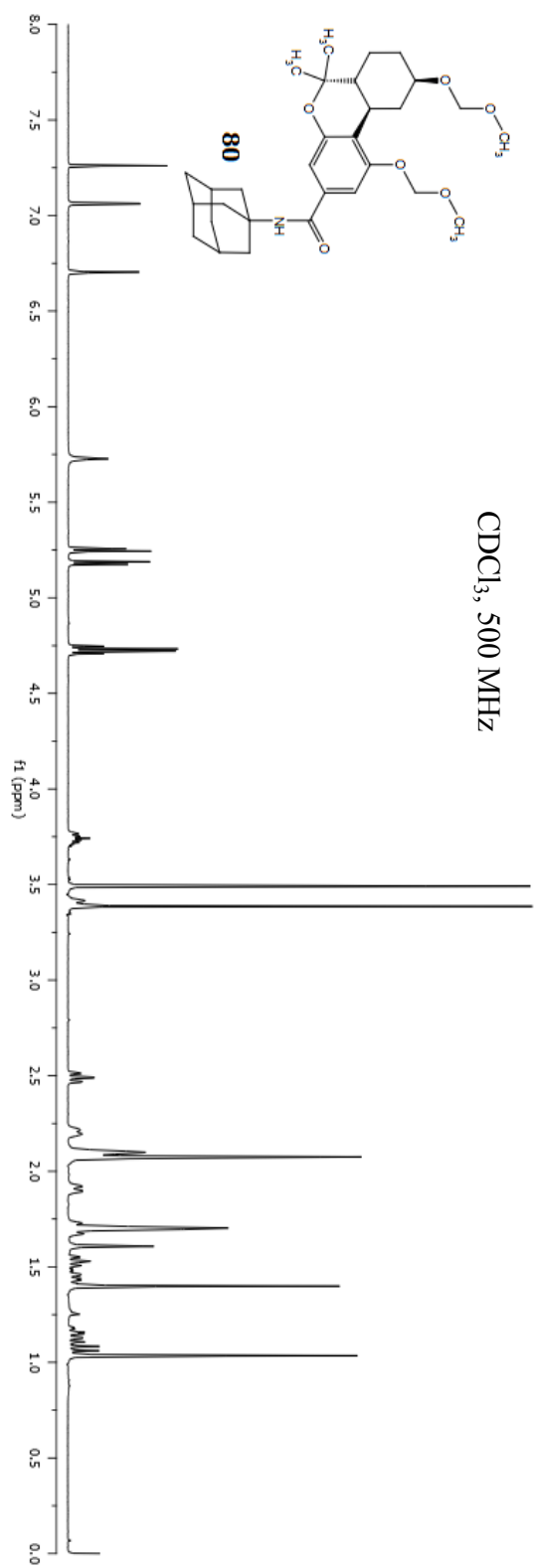


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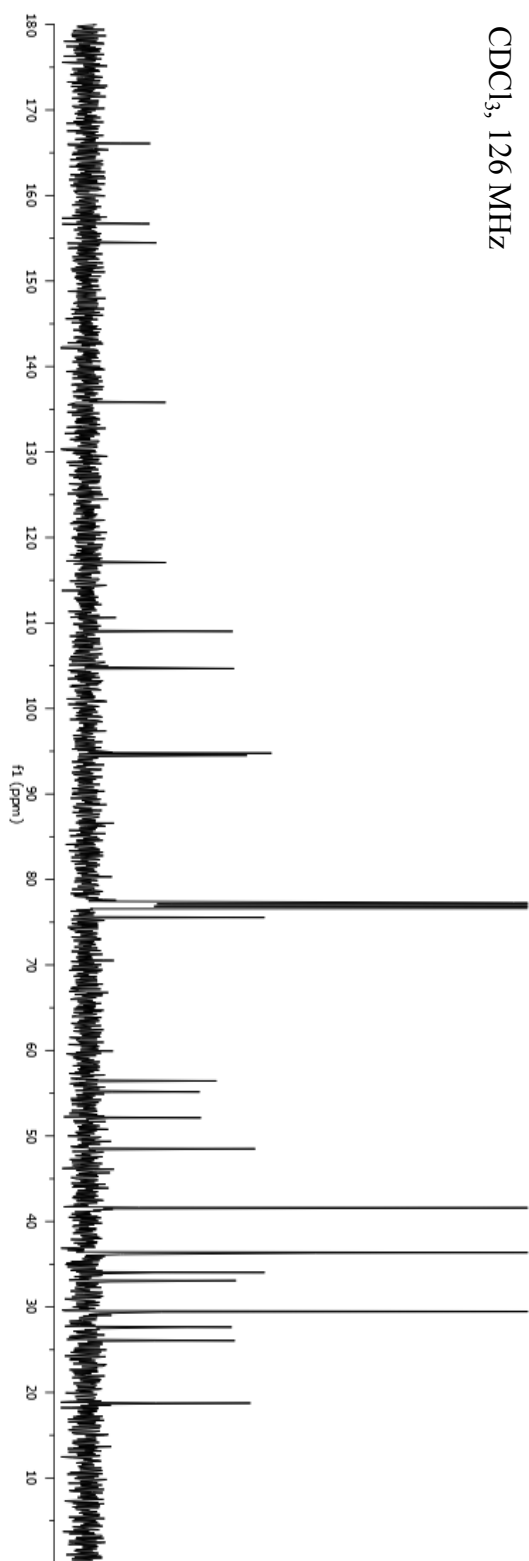


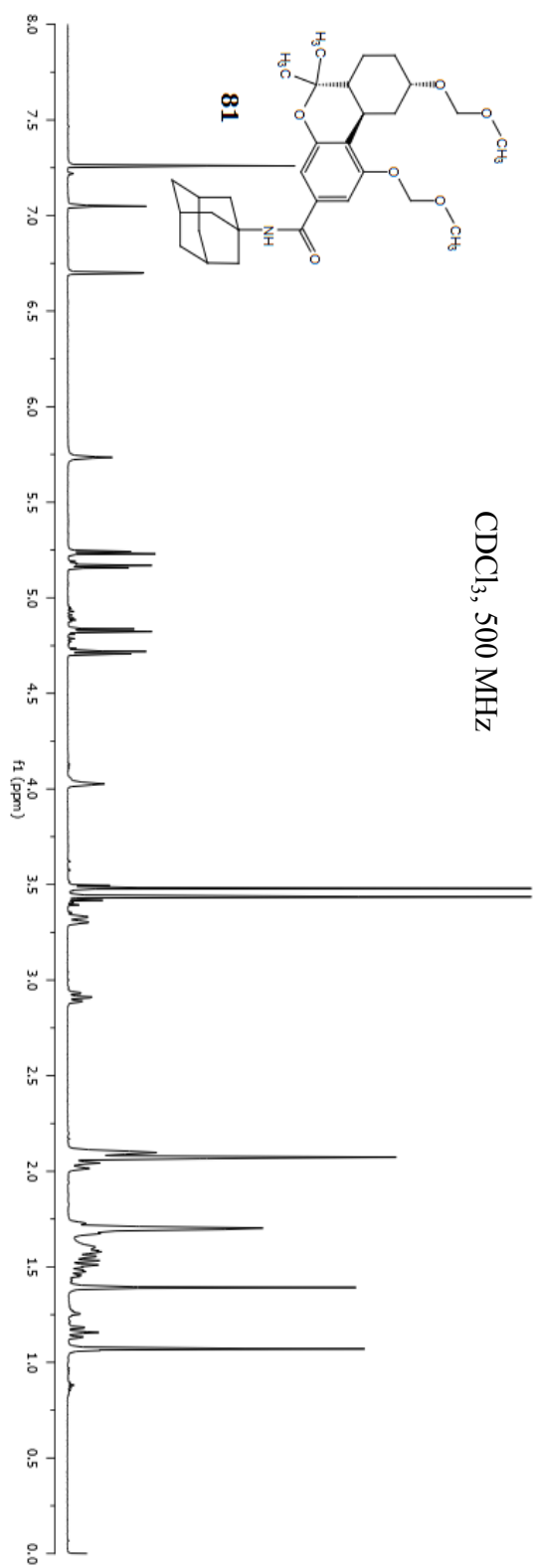


CDCl<sub>3</sub>, 500 MHz

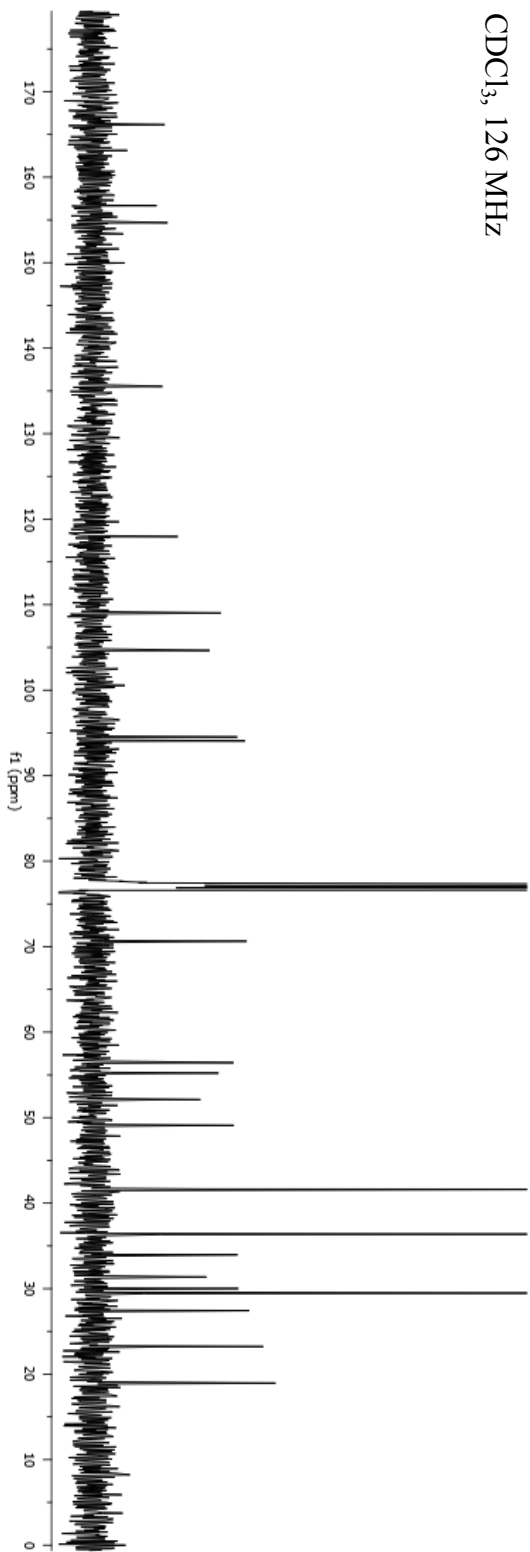


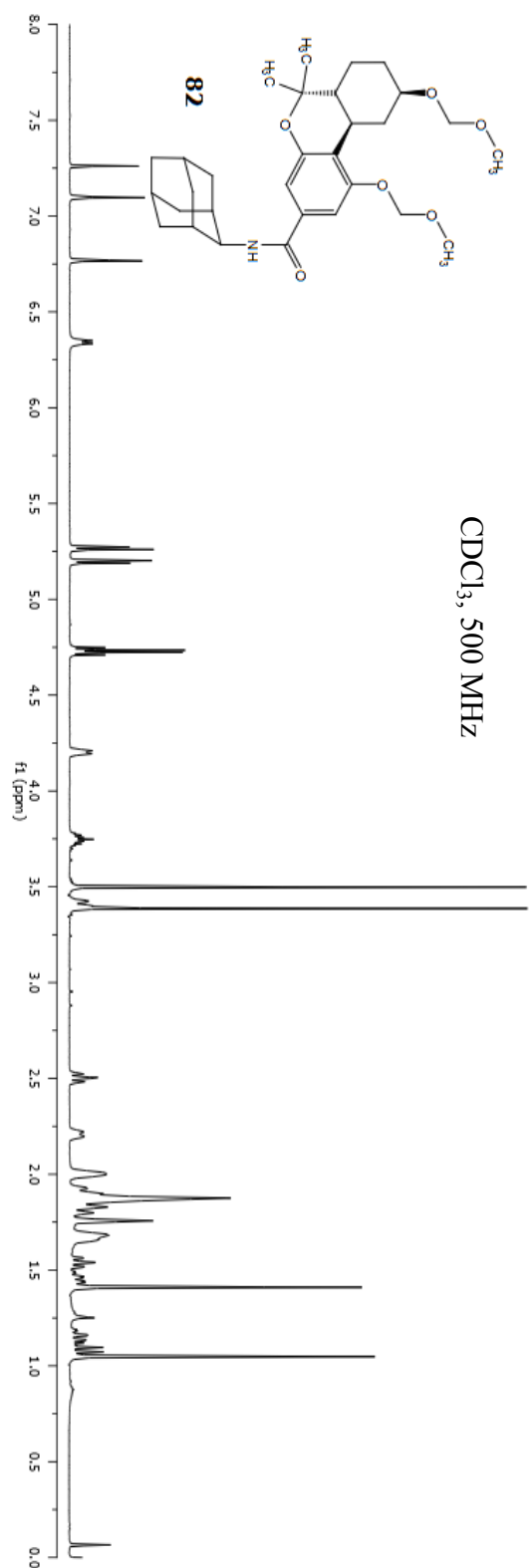
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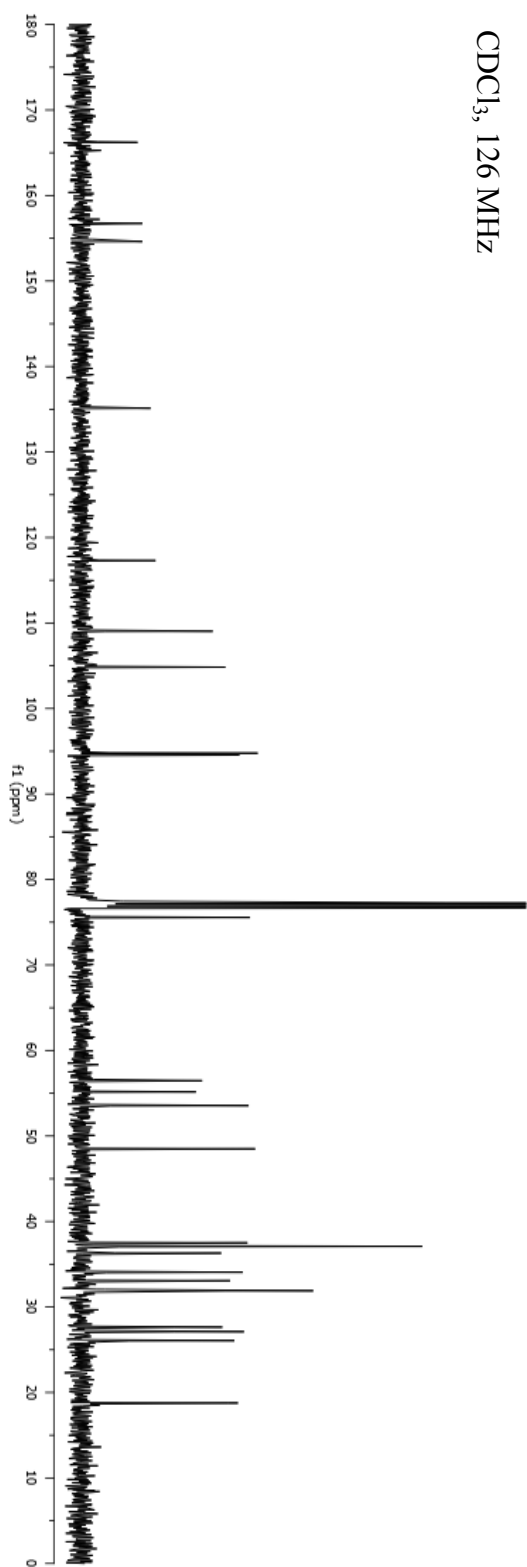


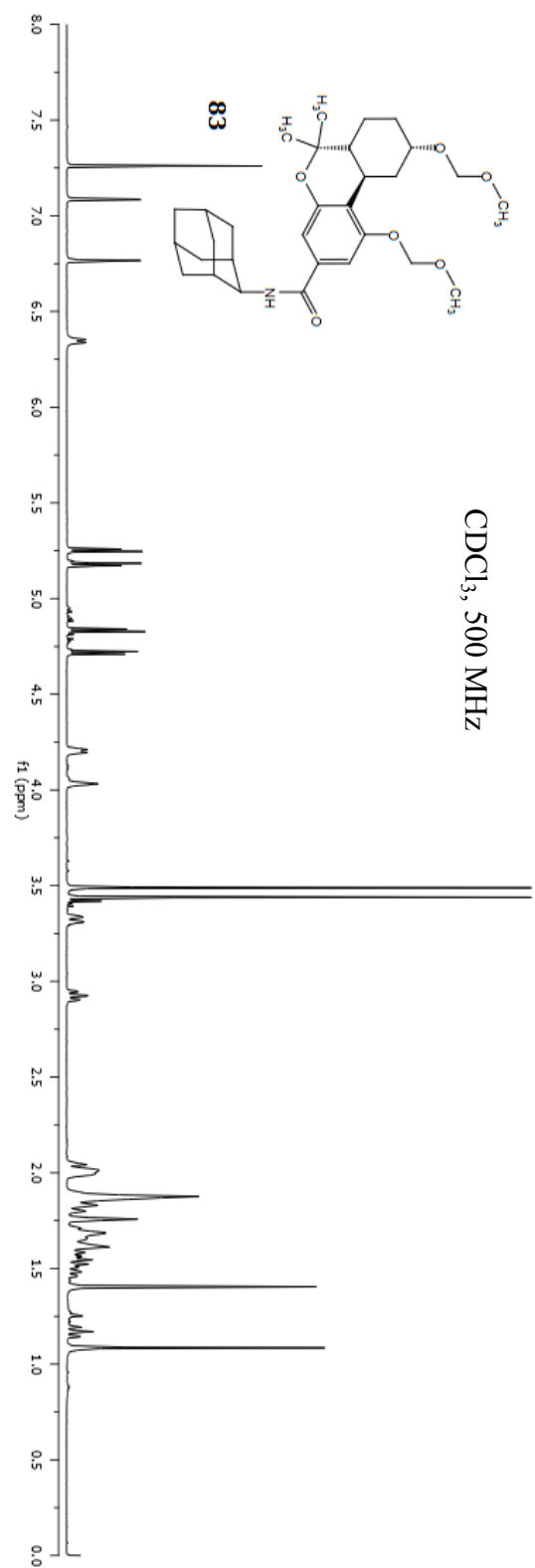
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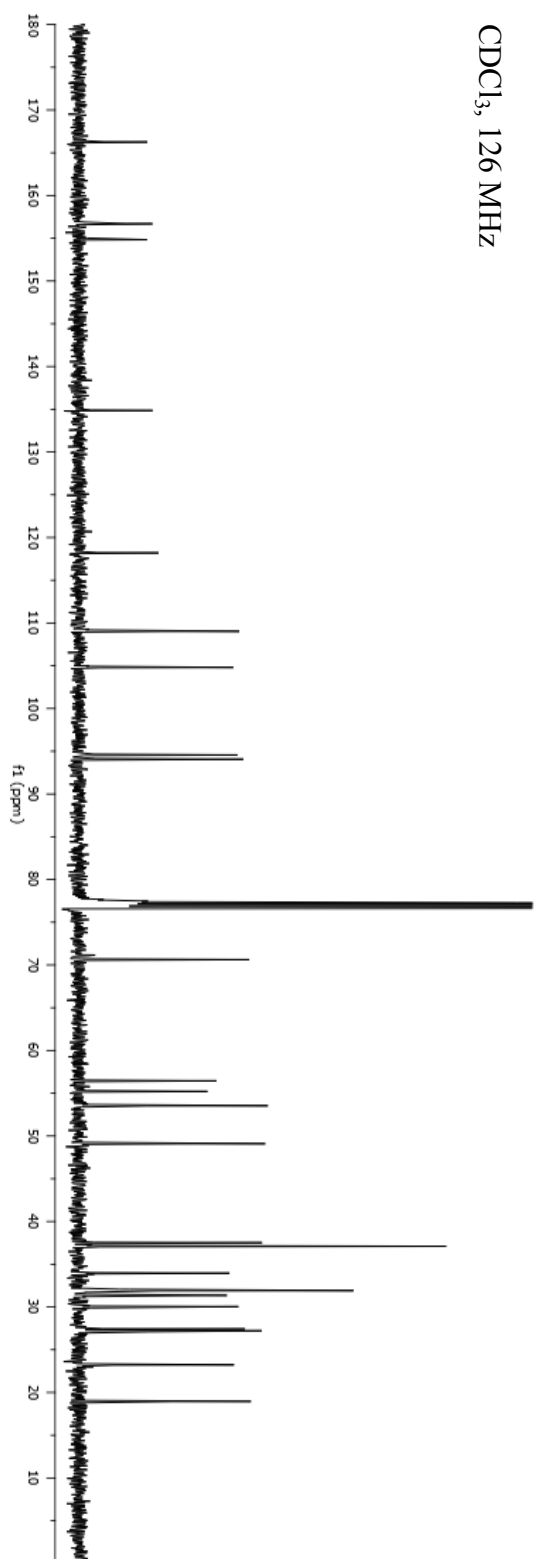


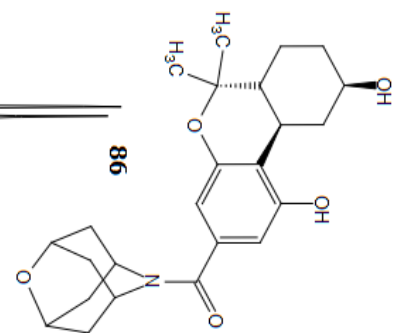
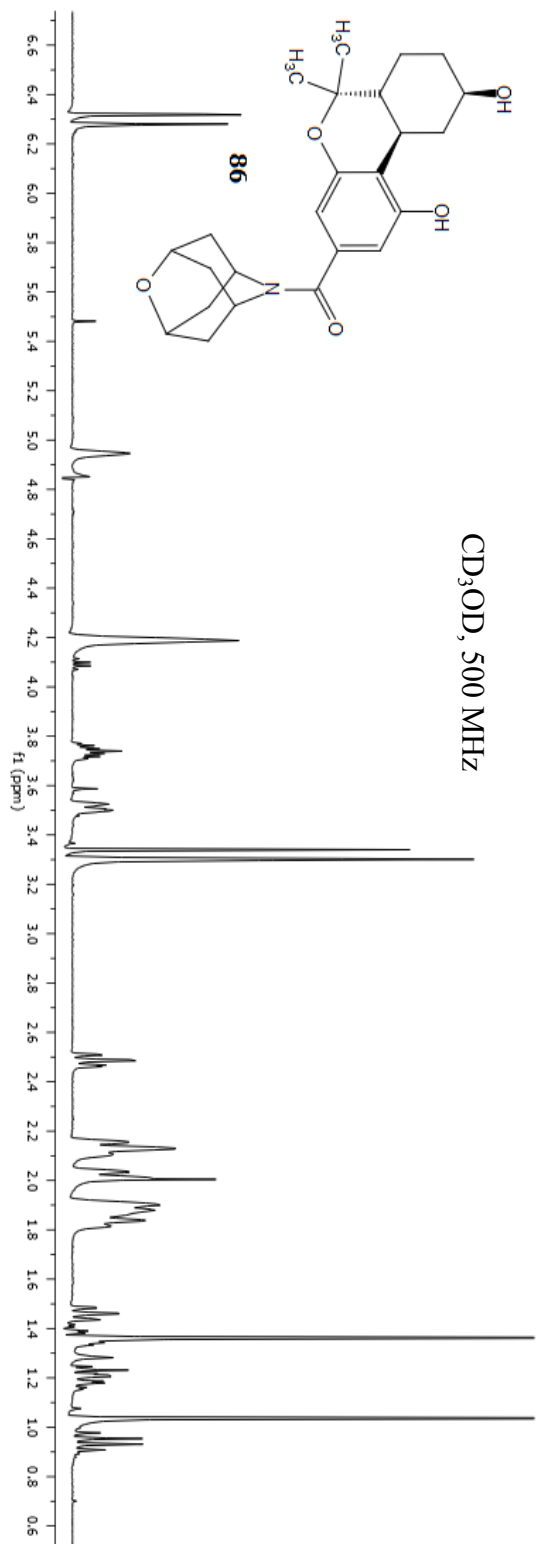
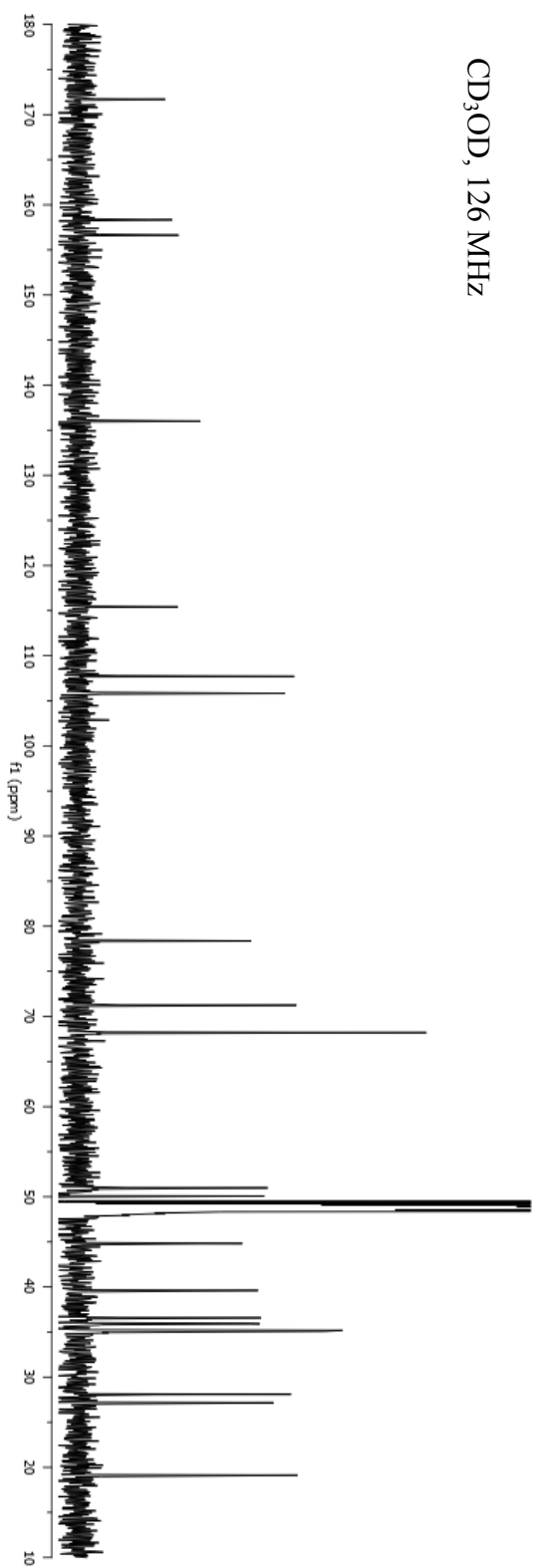
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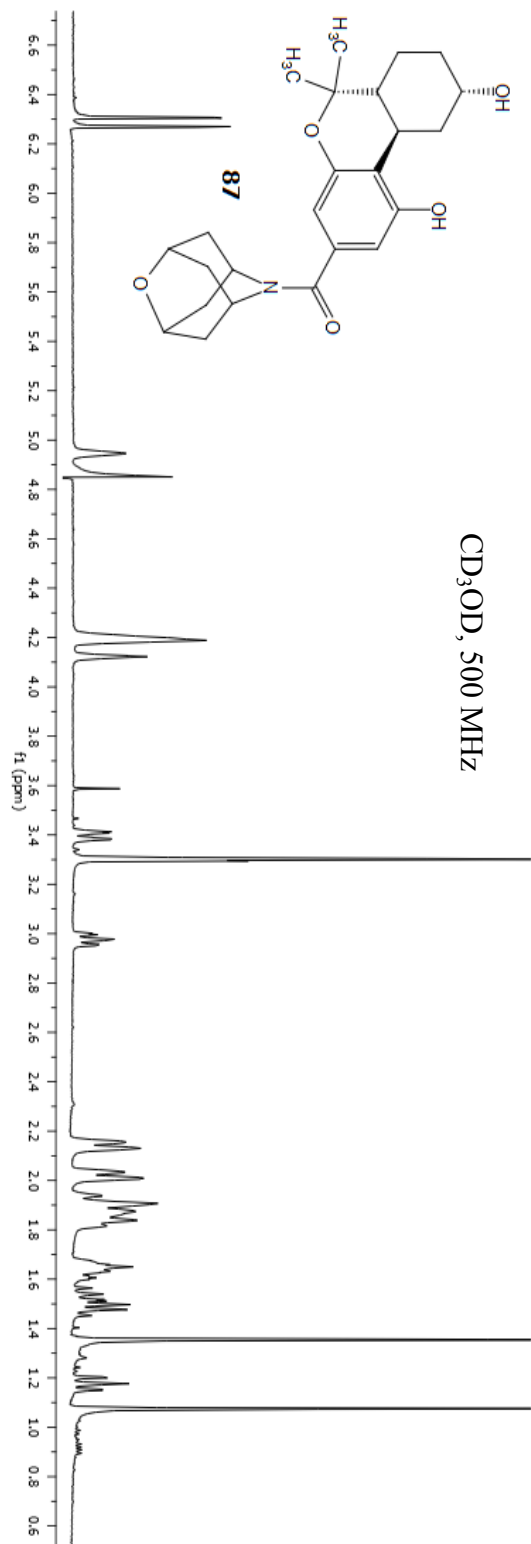
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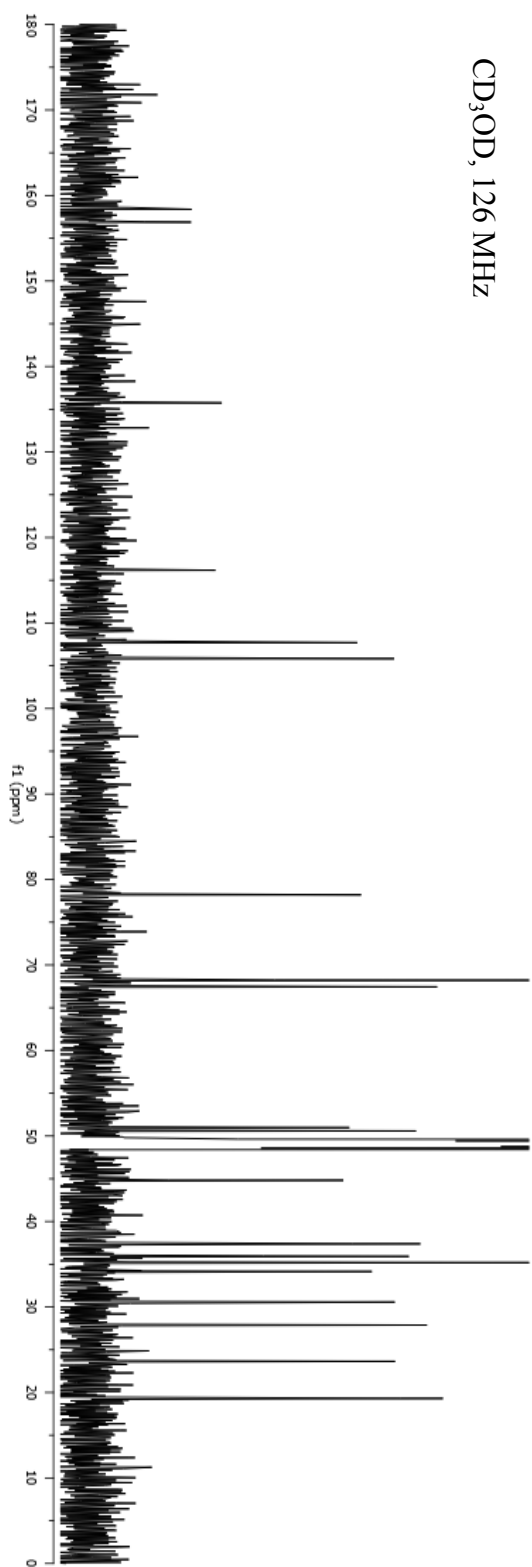
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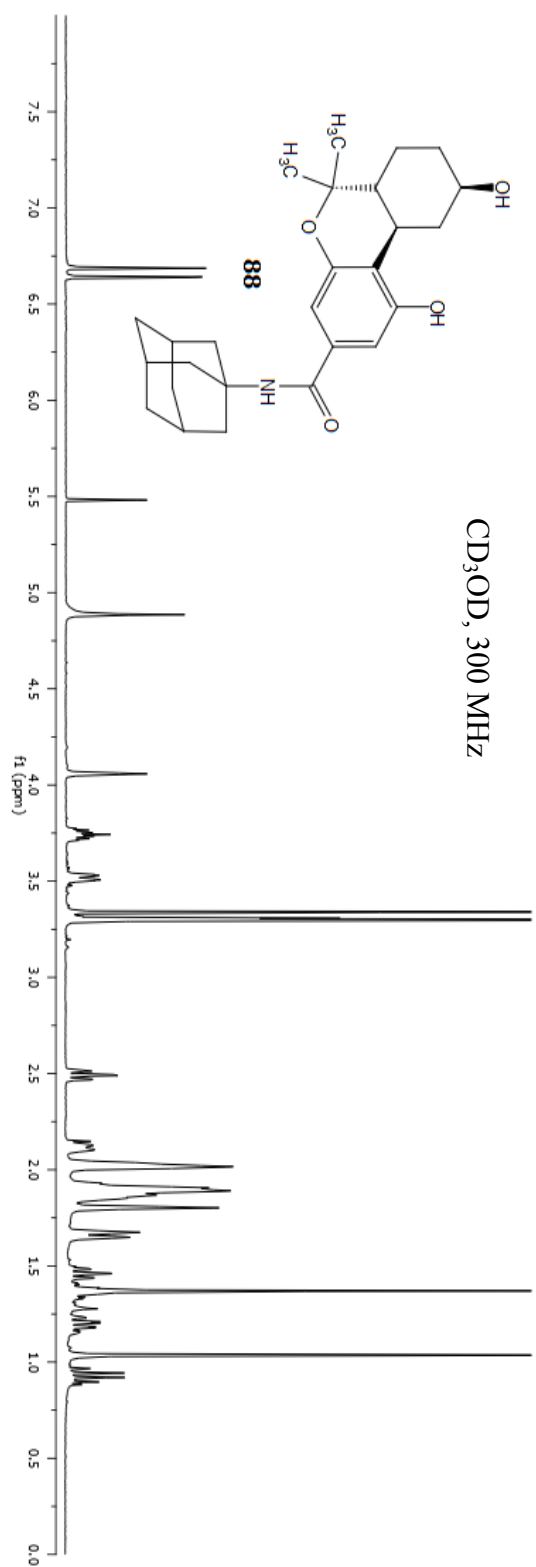


CD<sub>3</sub>OD, 500 MHz

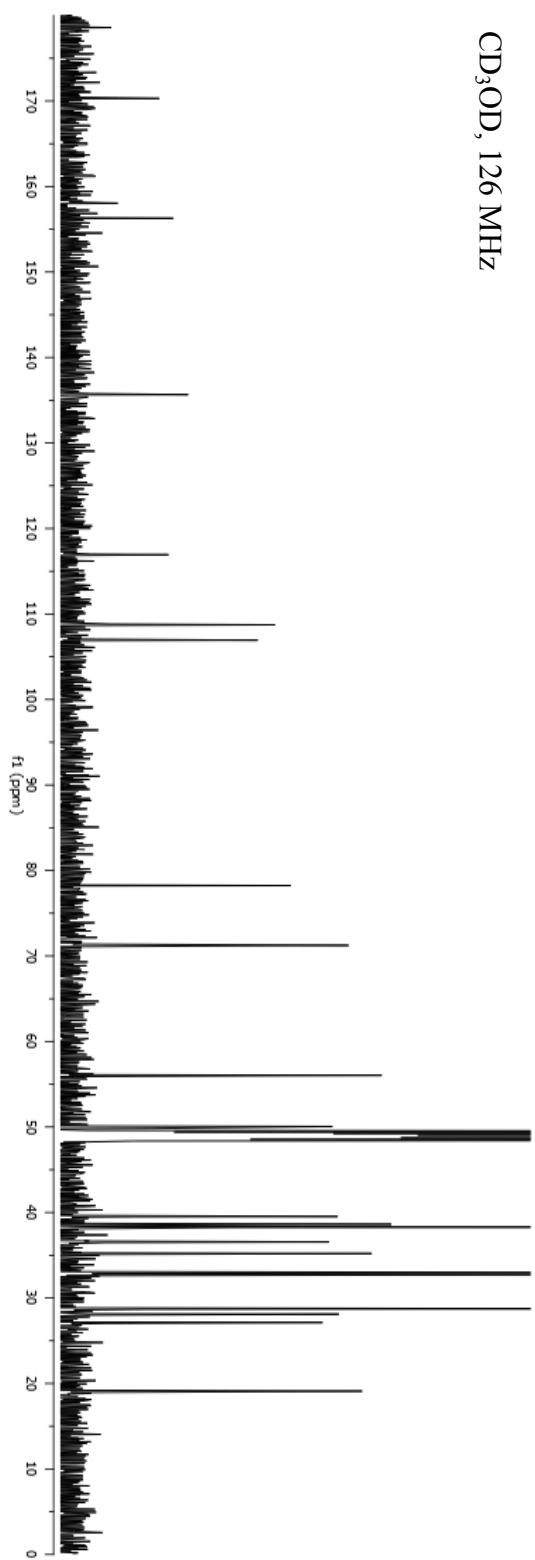


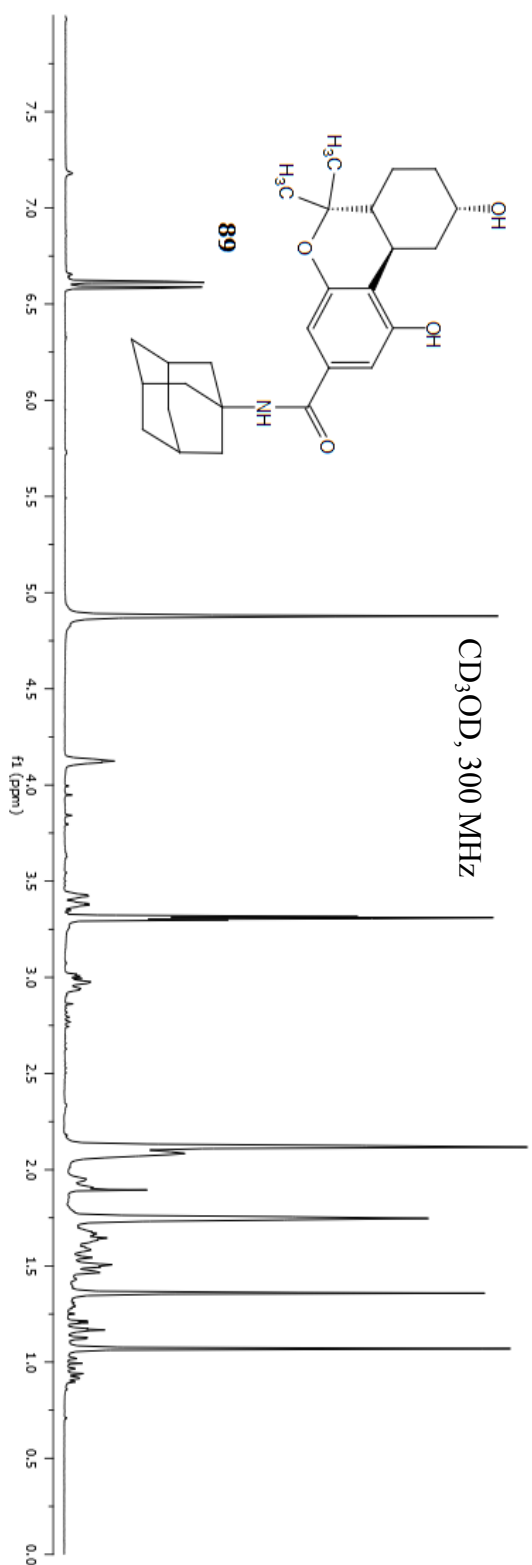
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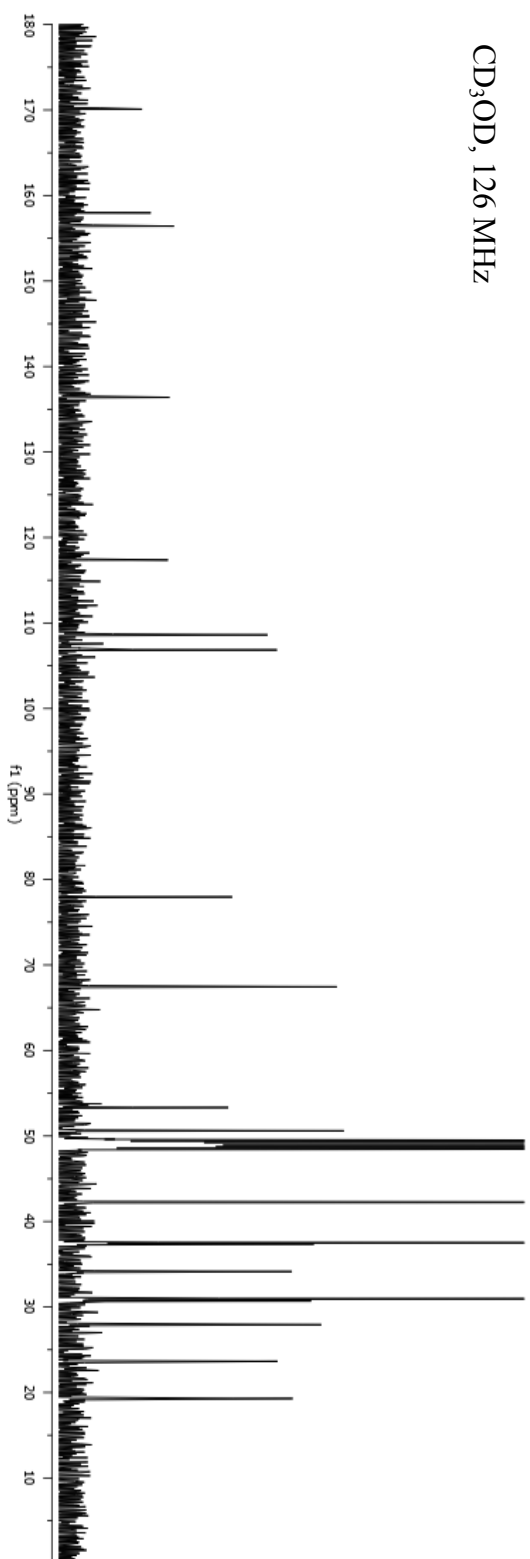


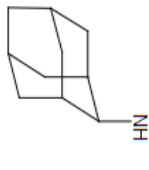
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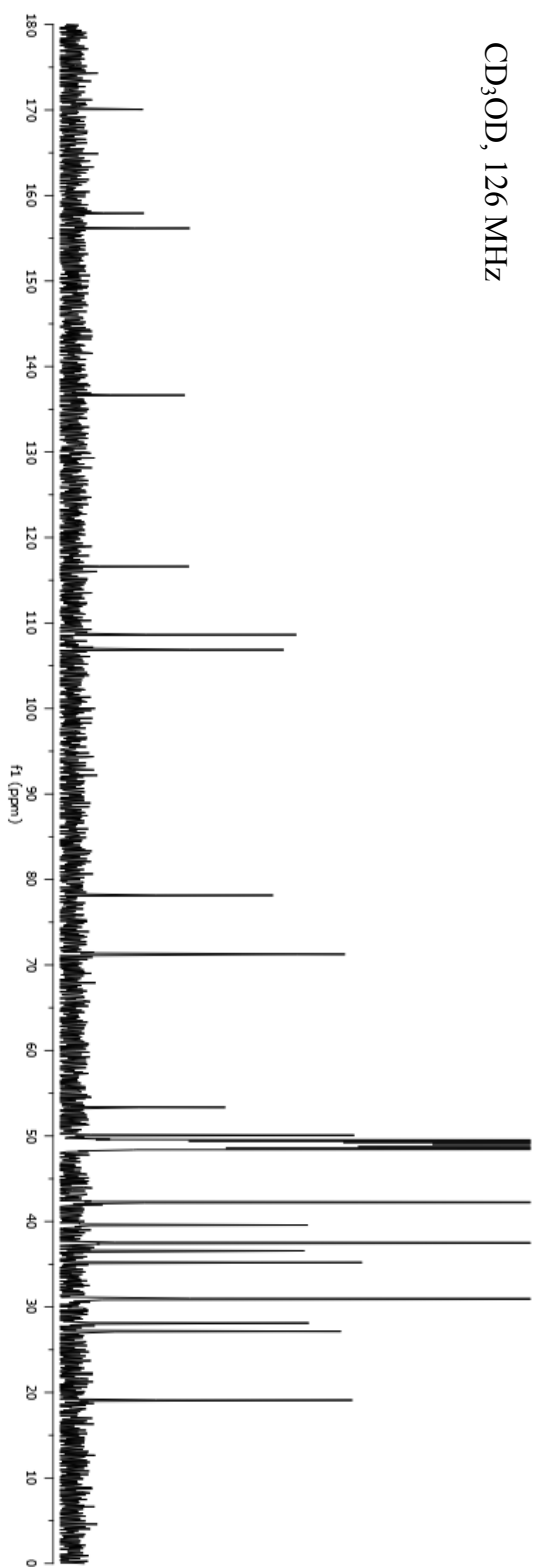


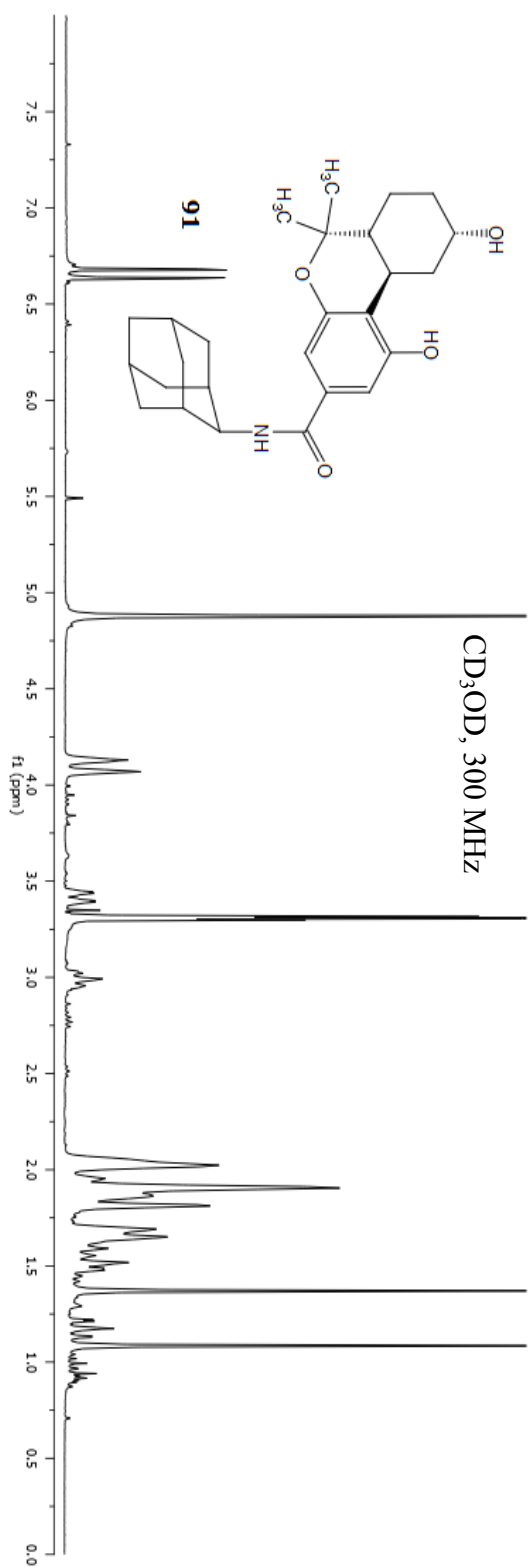
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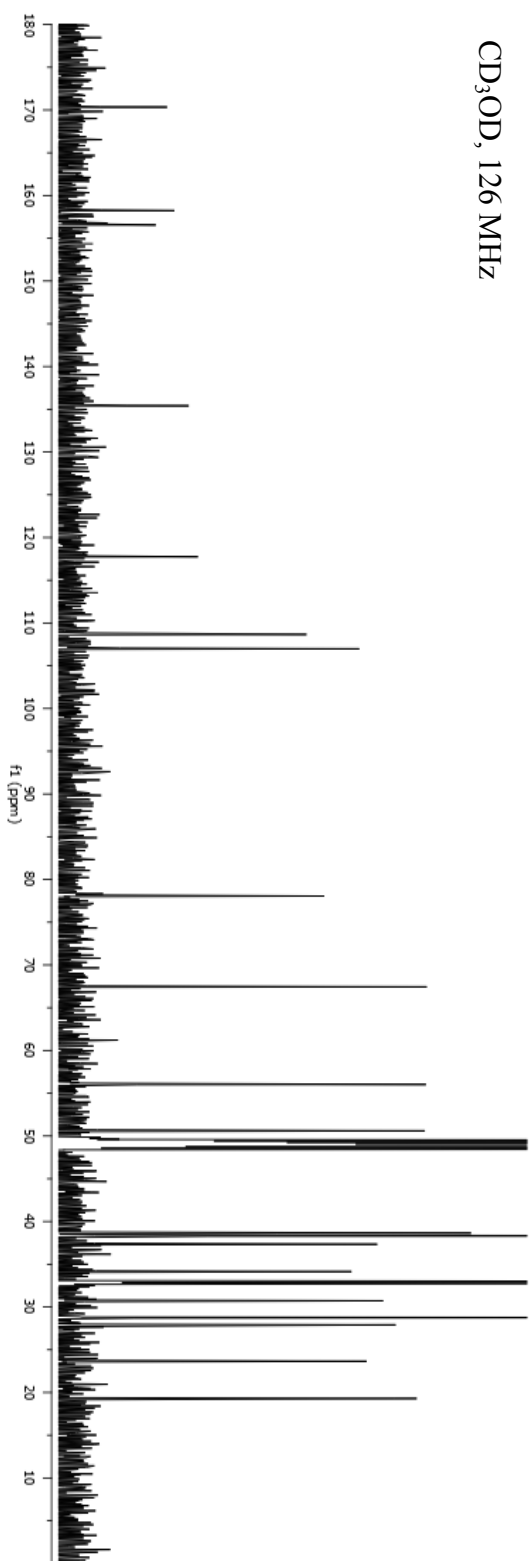


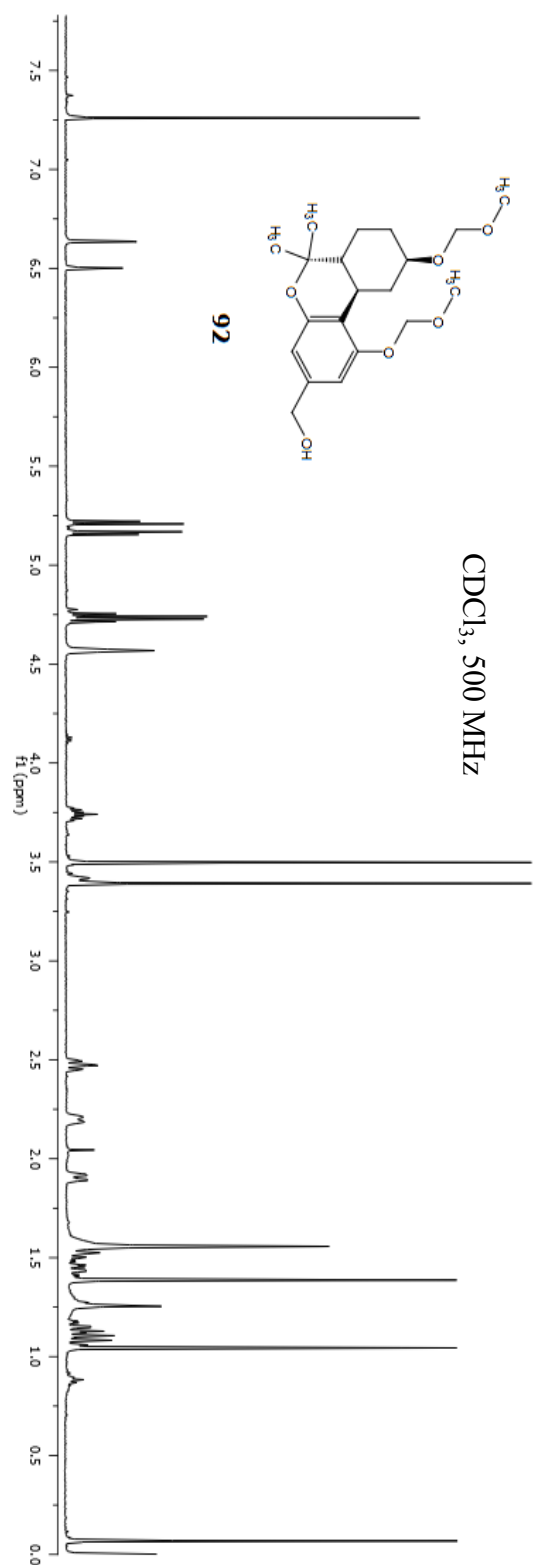
152



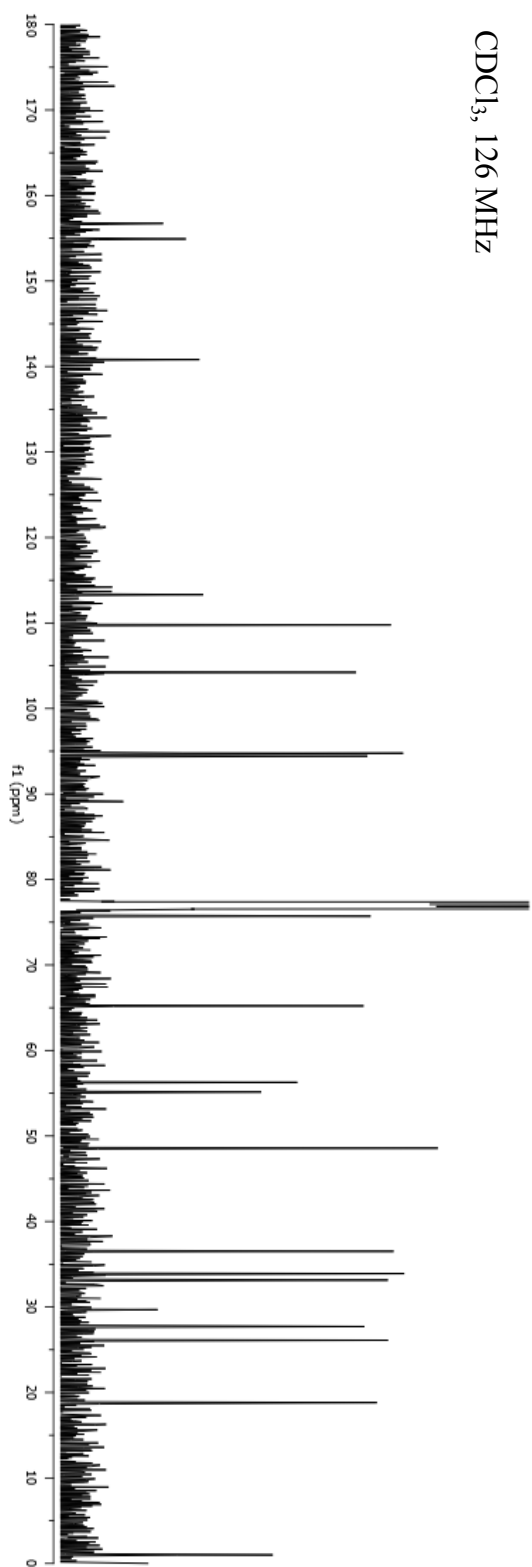


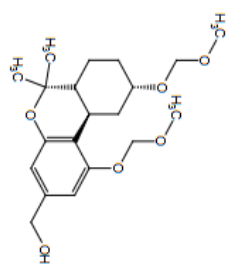
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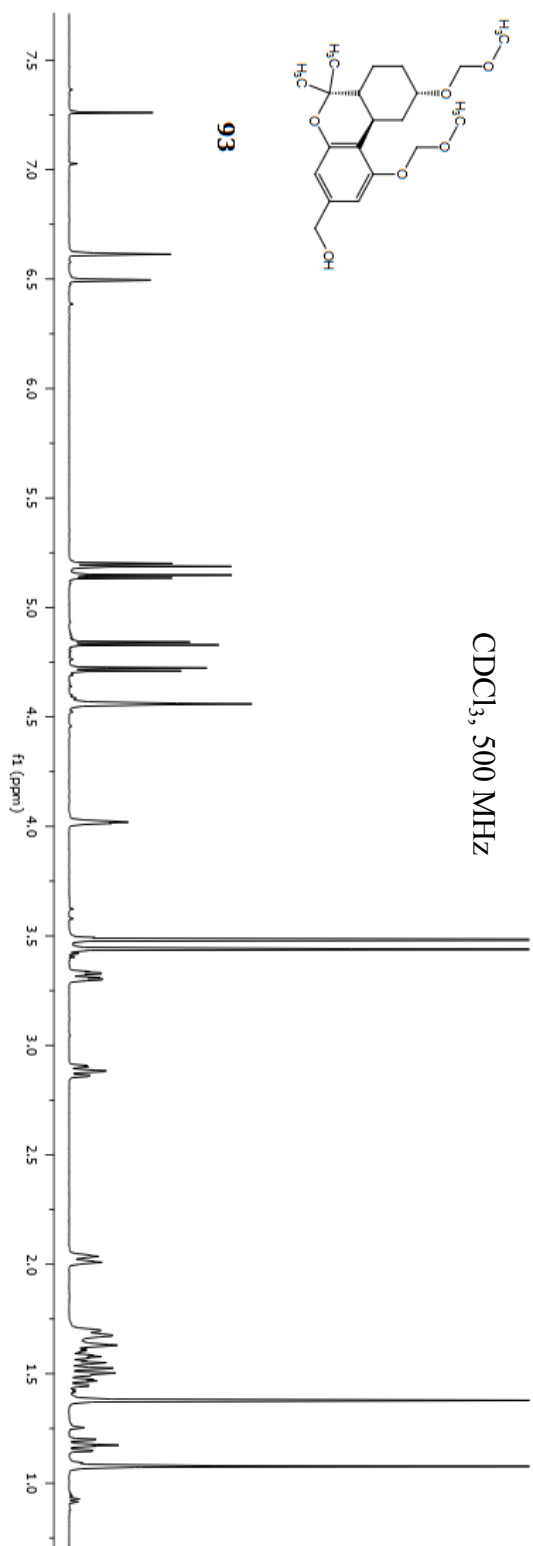
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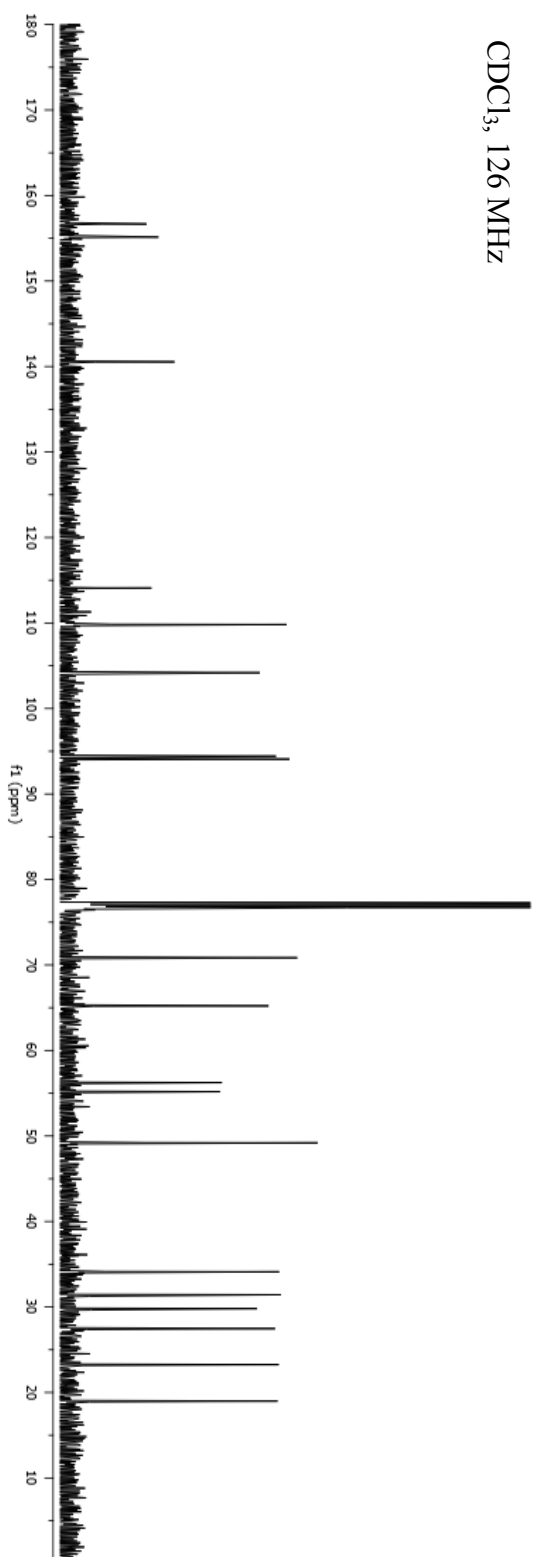


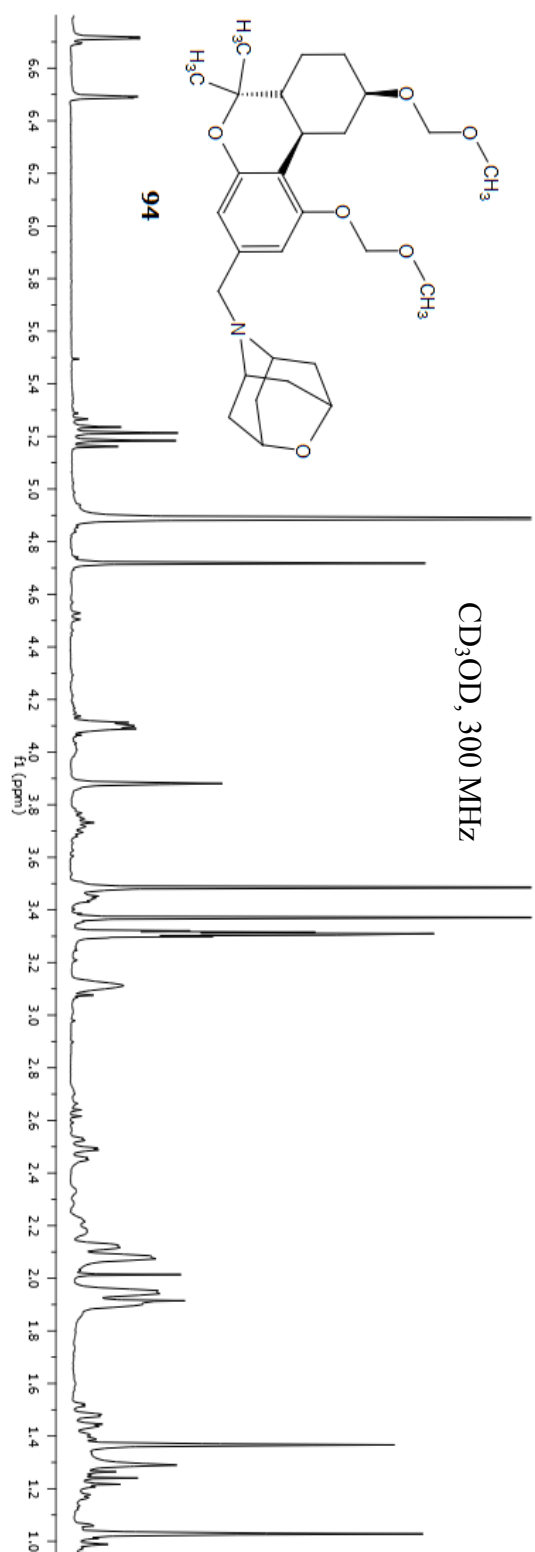
**93**

CDCl<sub>3</sub>, 500 MHz

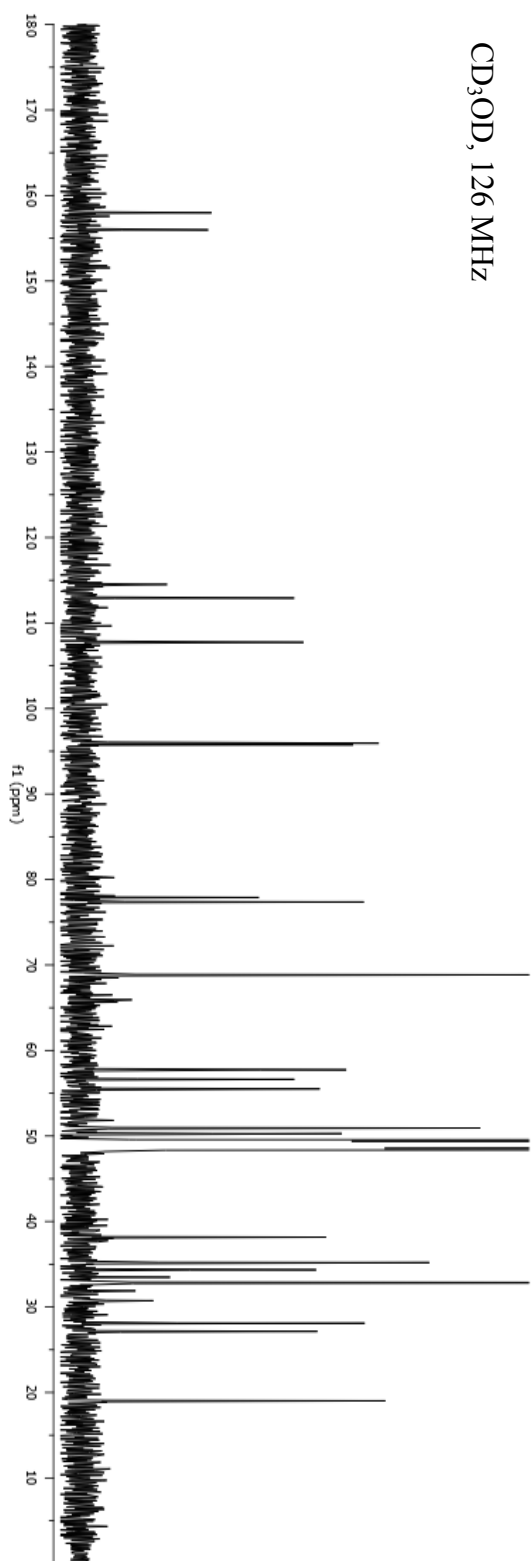


CDCl<sub>3</sub>, 126 MHz

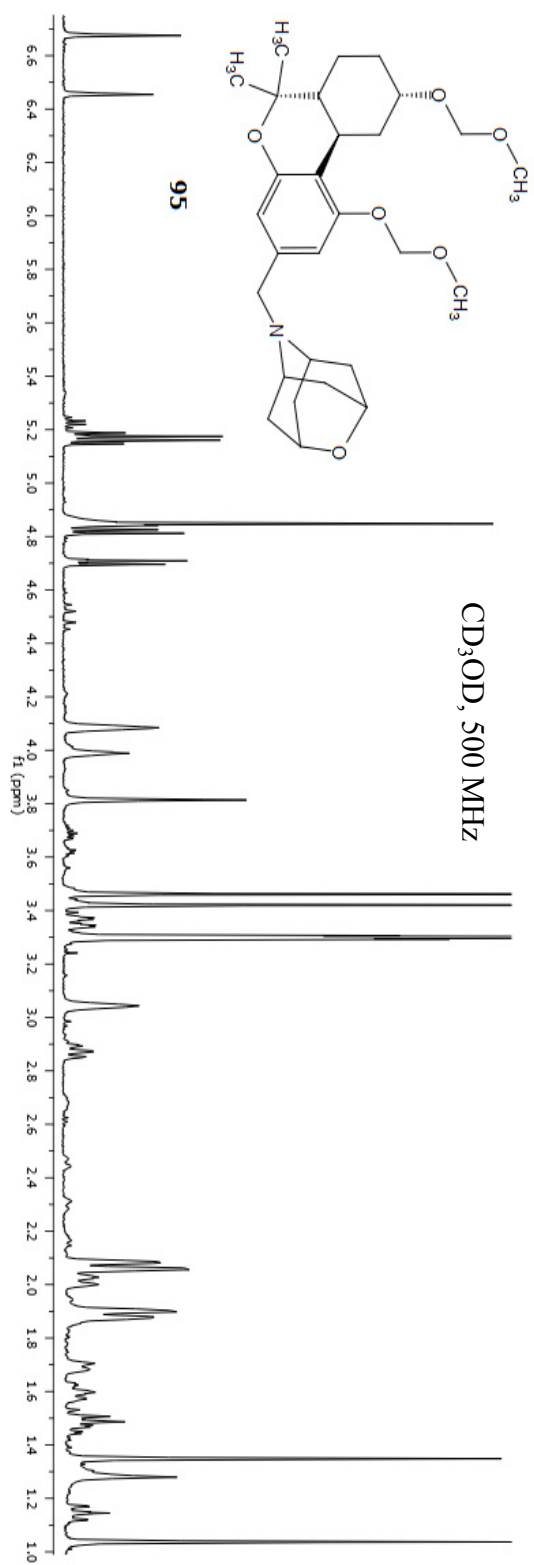




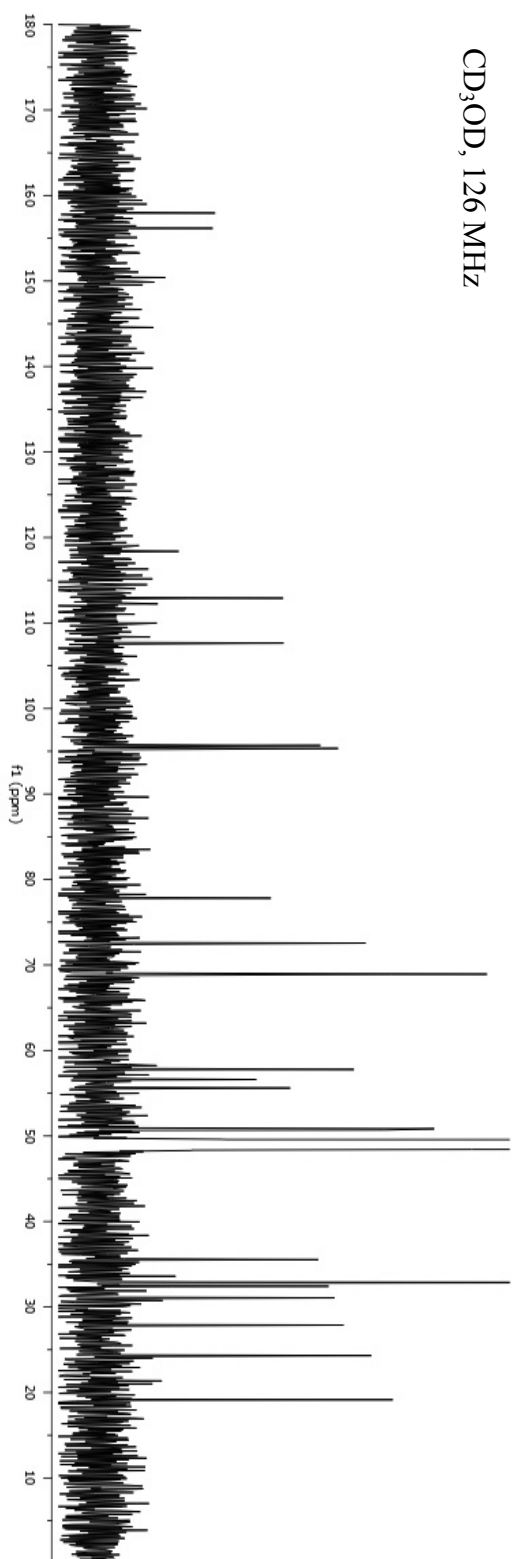
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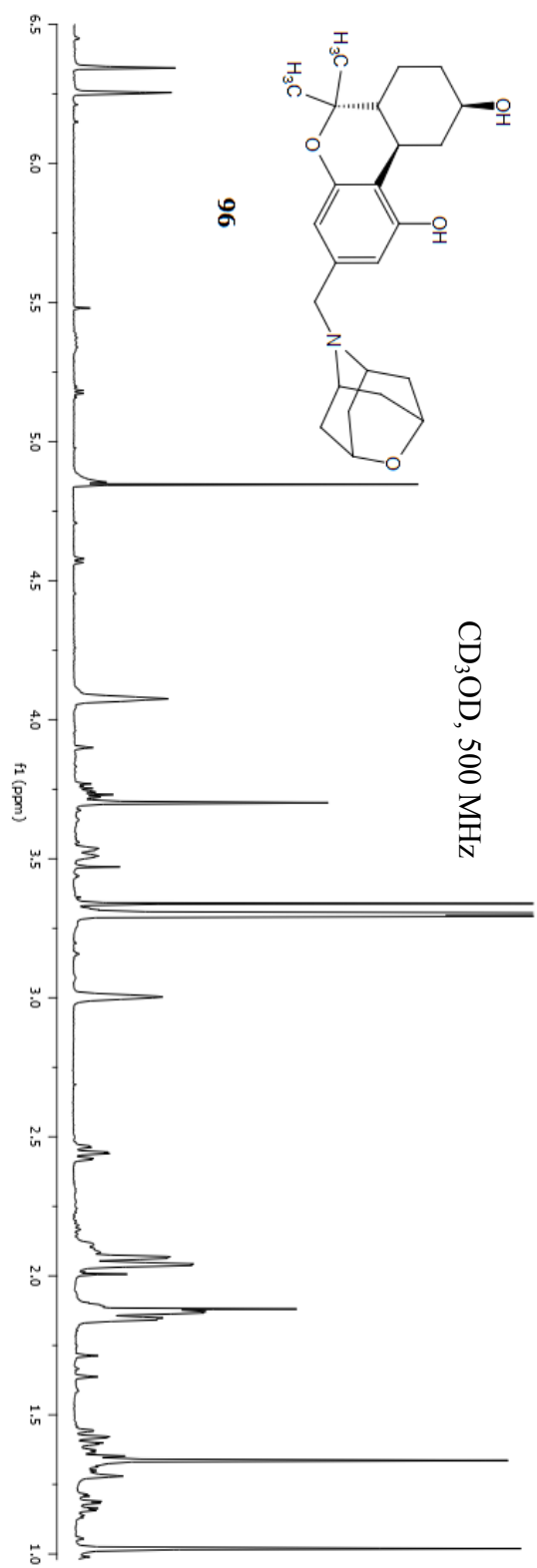




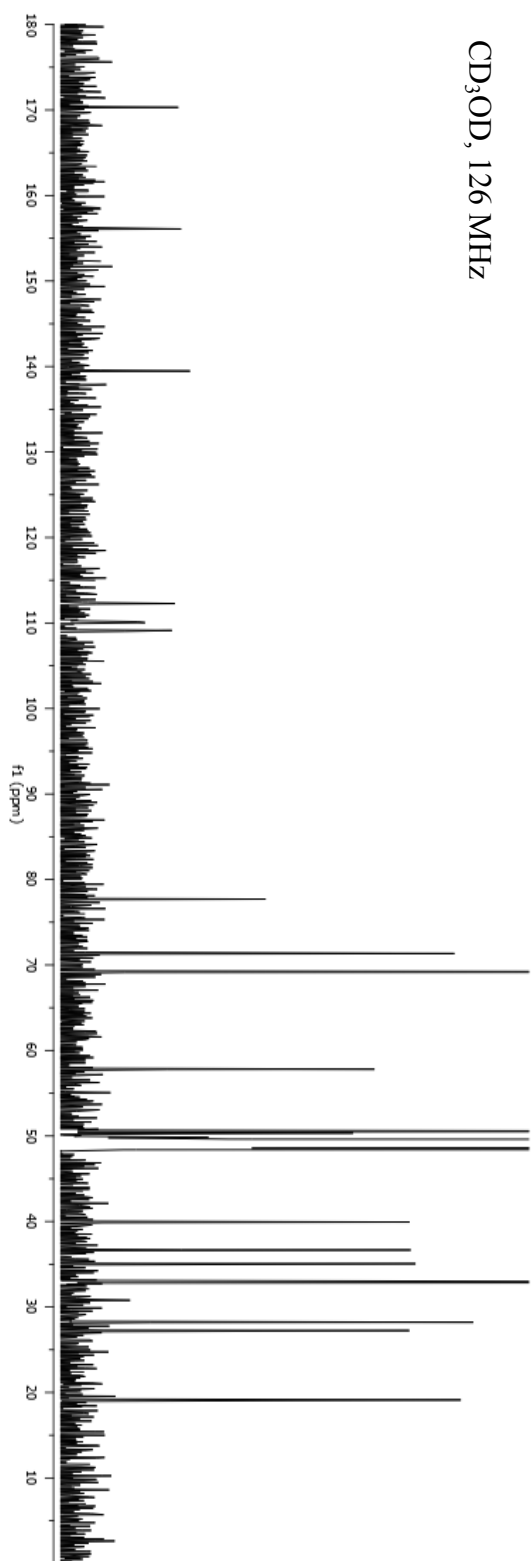


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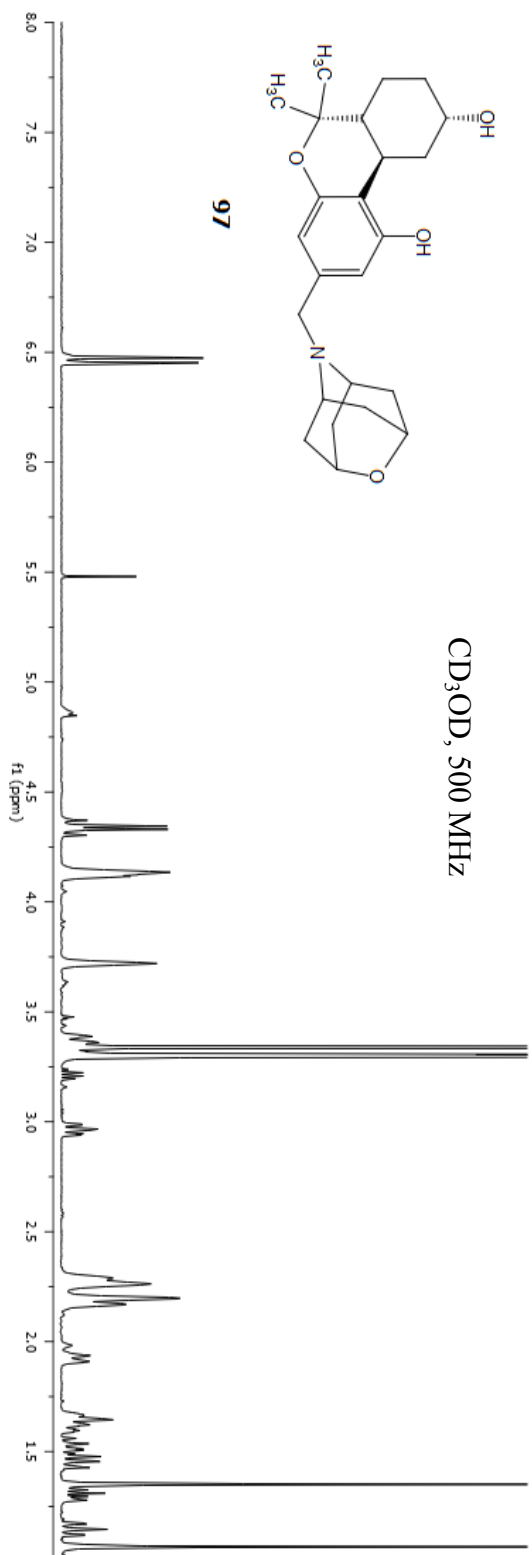
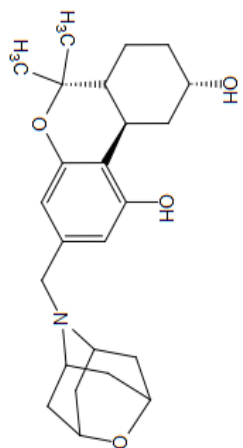




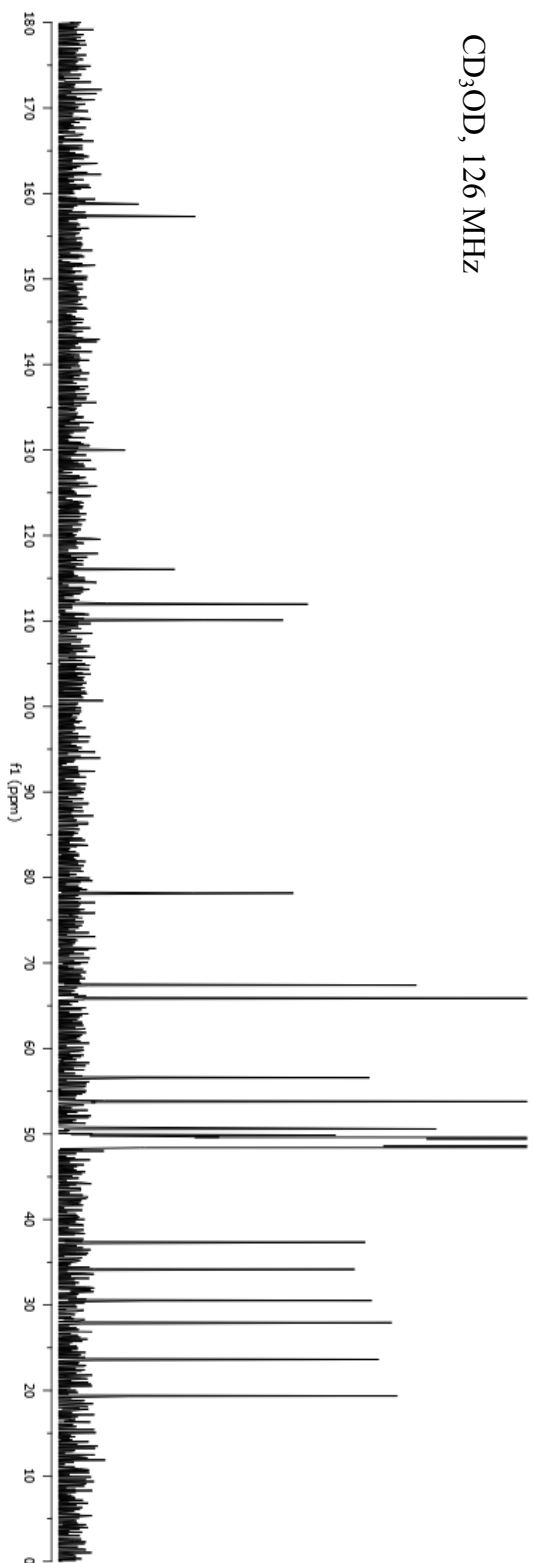
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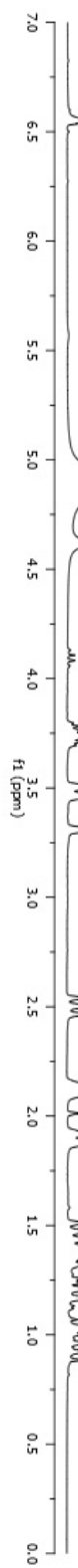
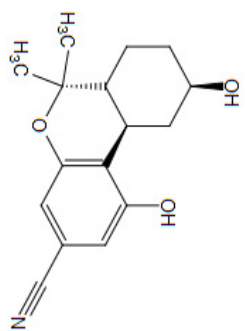
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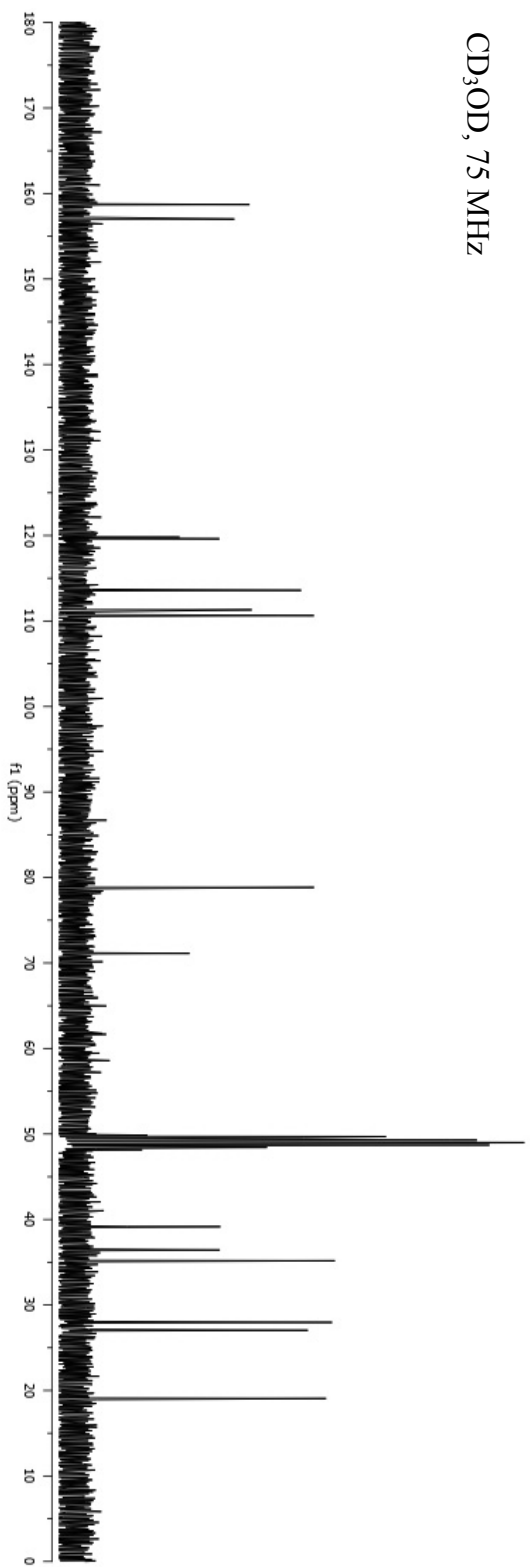
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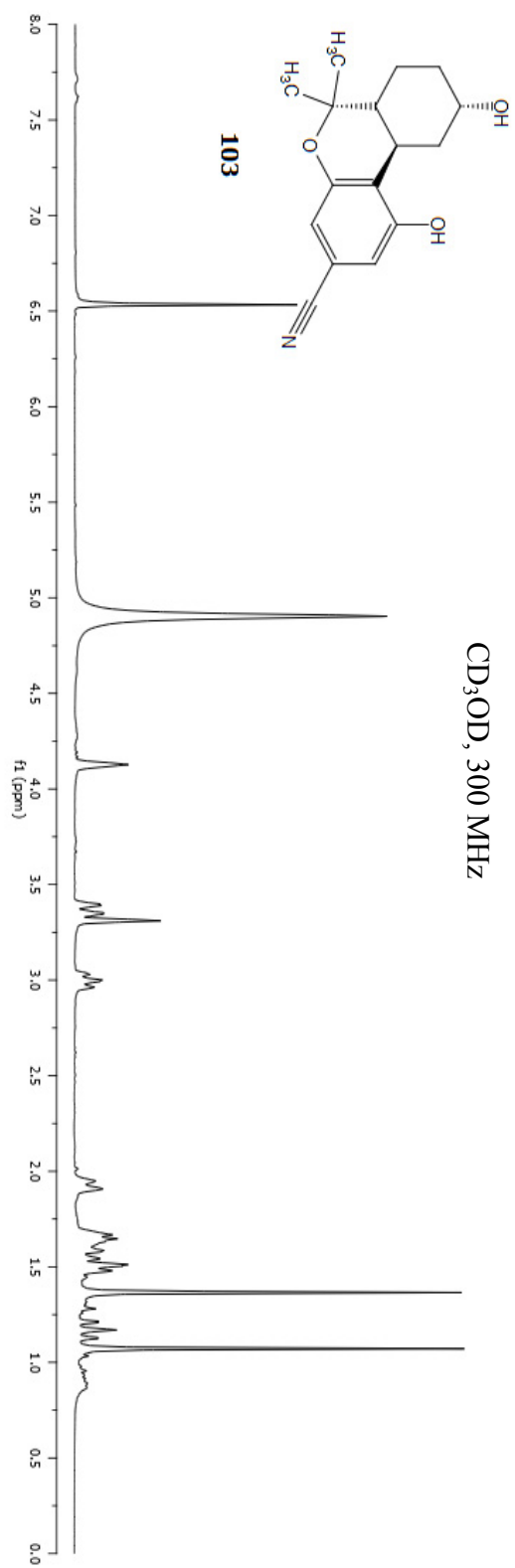
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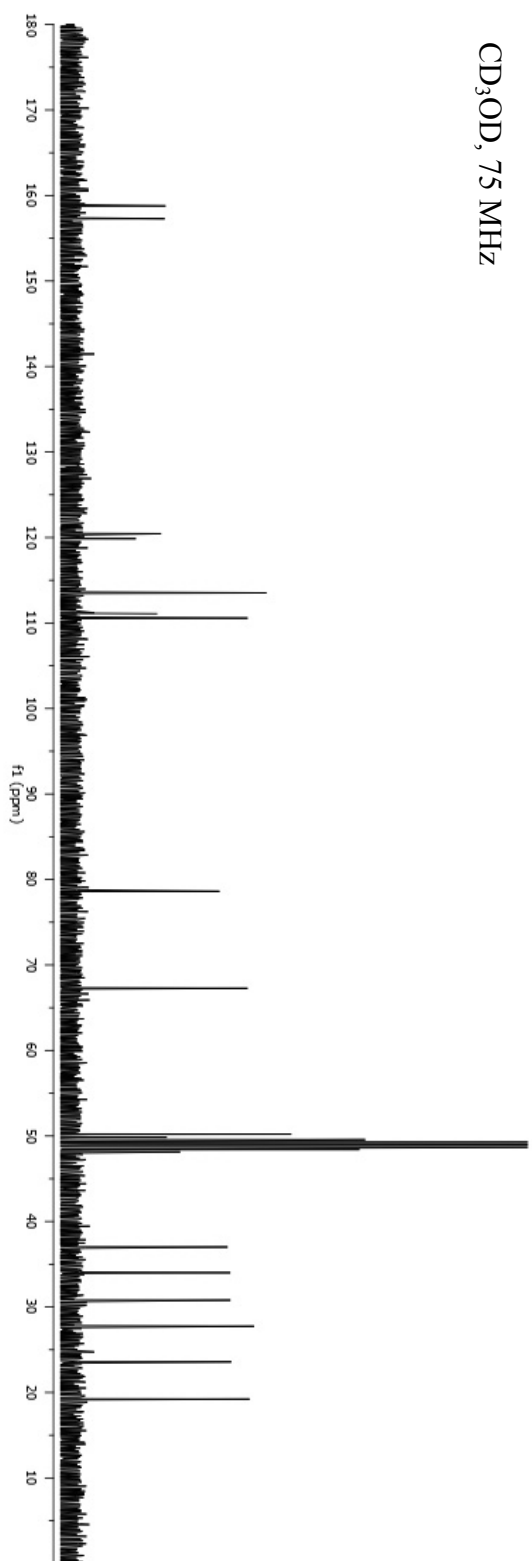
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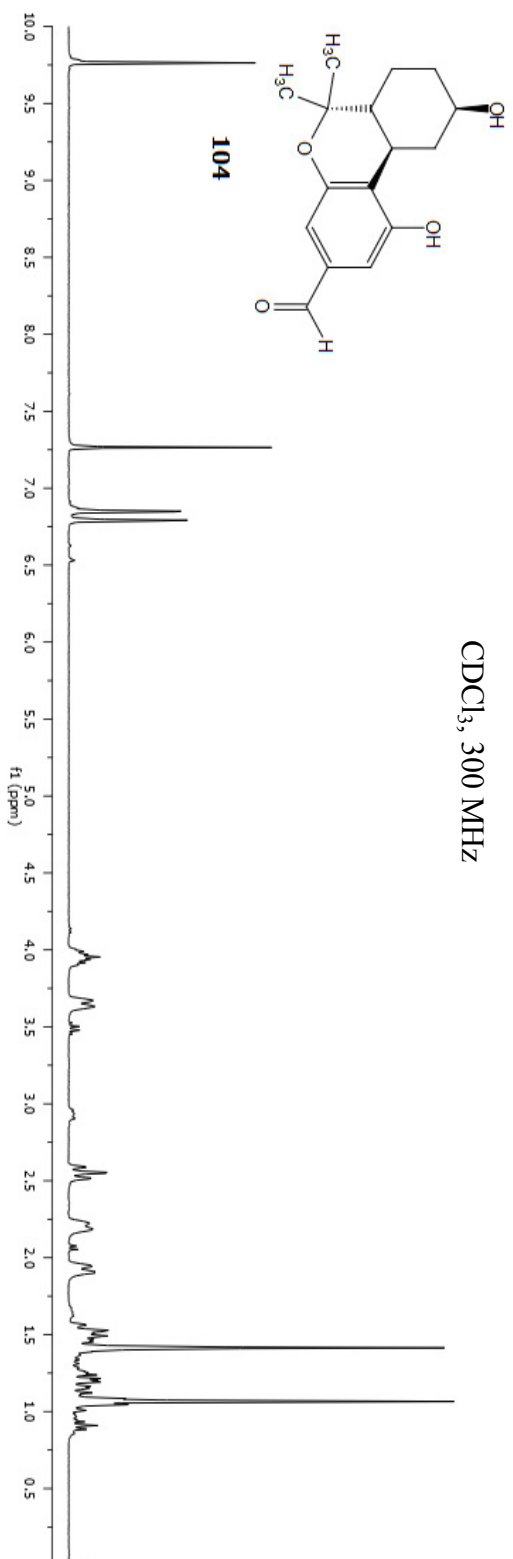
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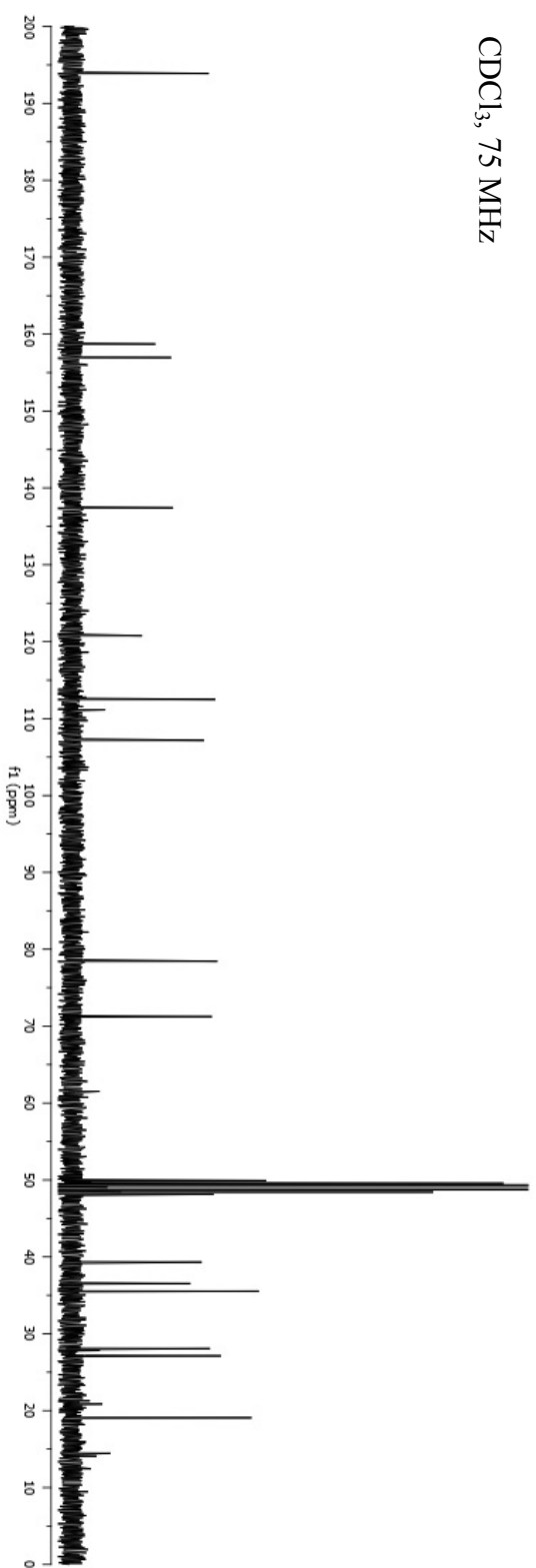
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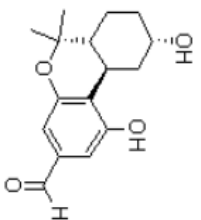


CDCl<sub>3</sub>, 300 MHz



CDCl<sub>3</sub>, 75 MHz

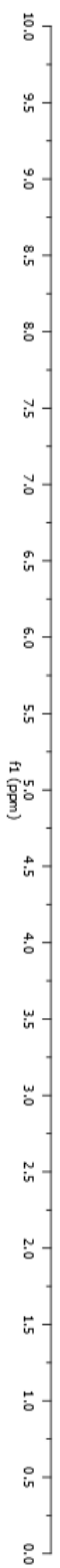




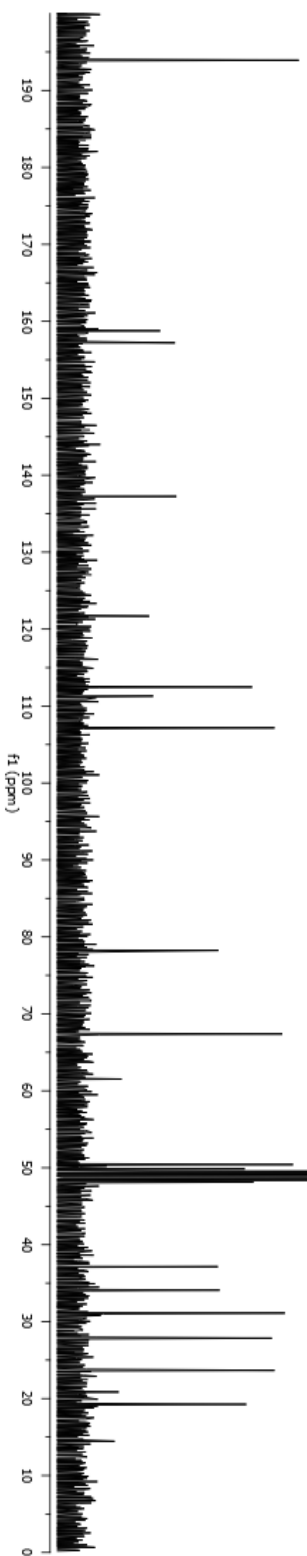
**105**

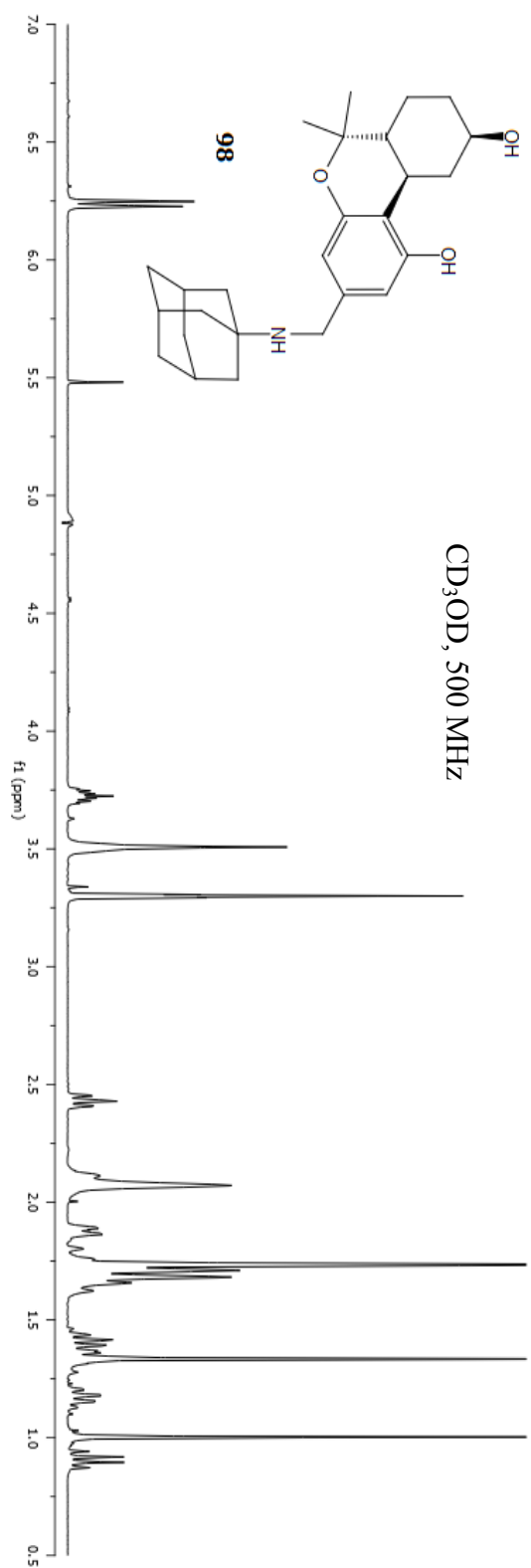
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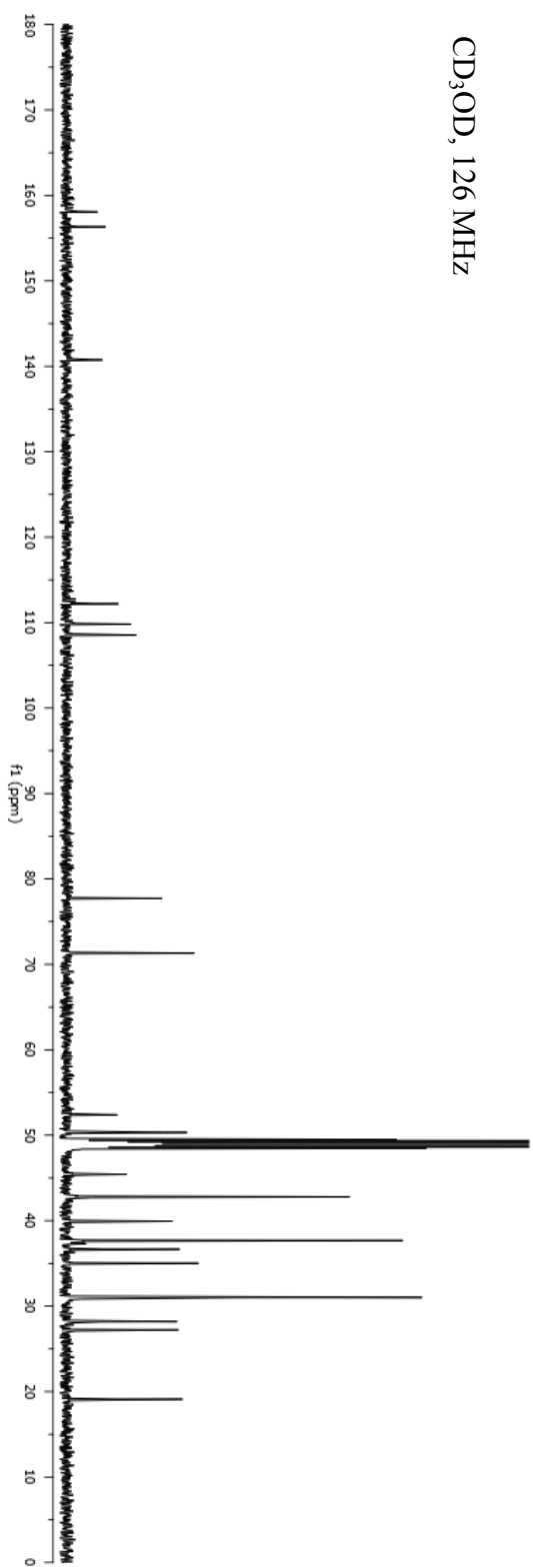


CD<sub>3</sub>OD, 75 MHz

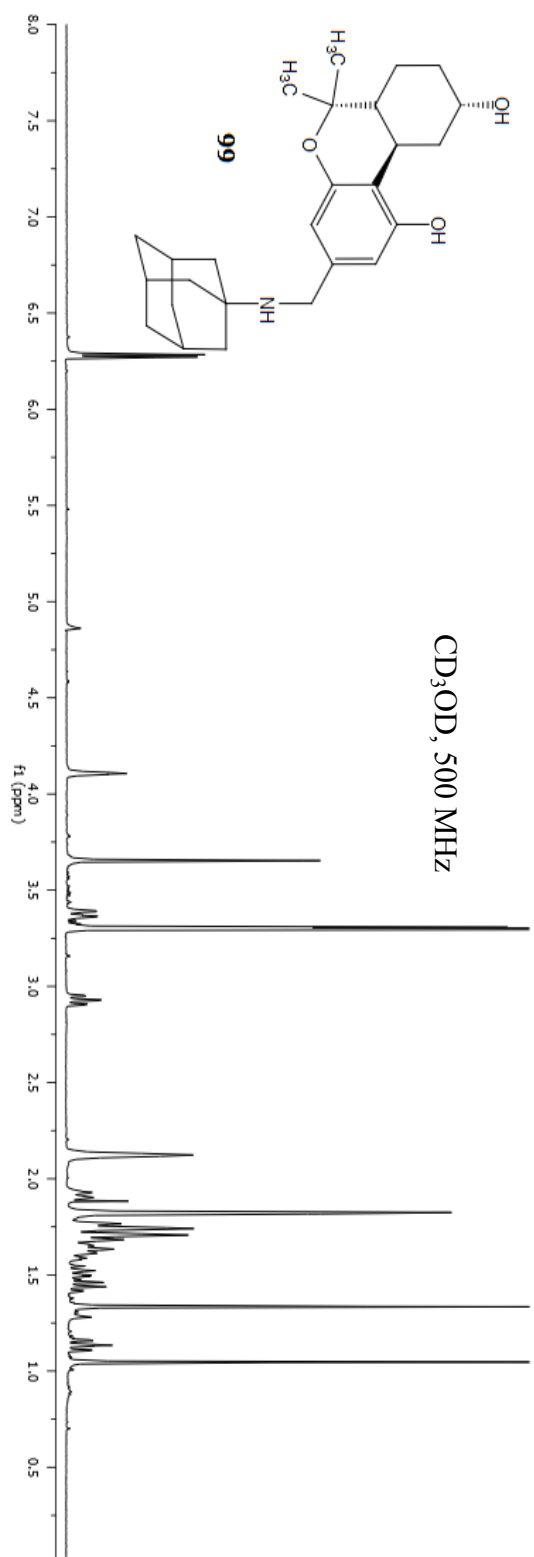




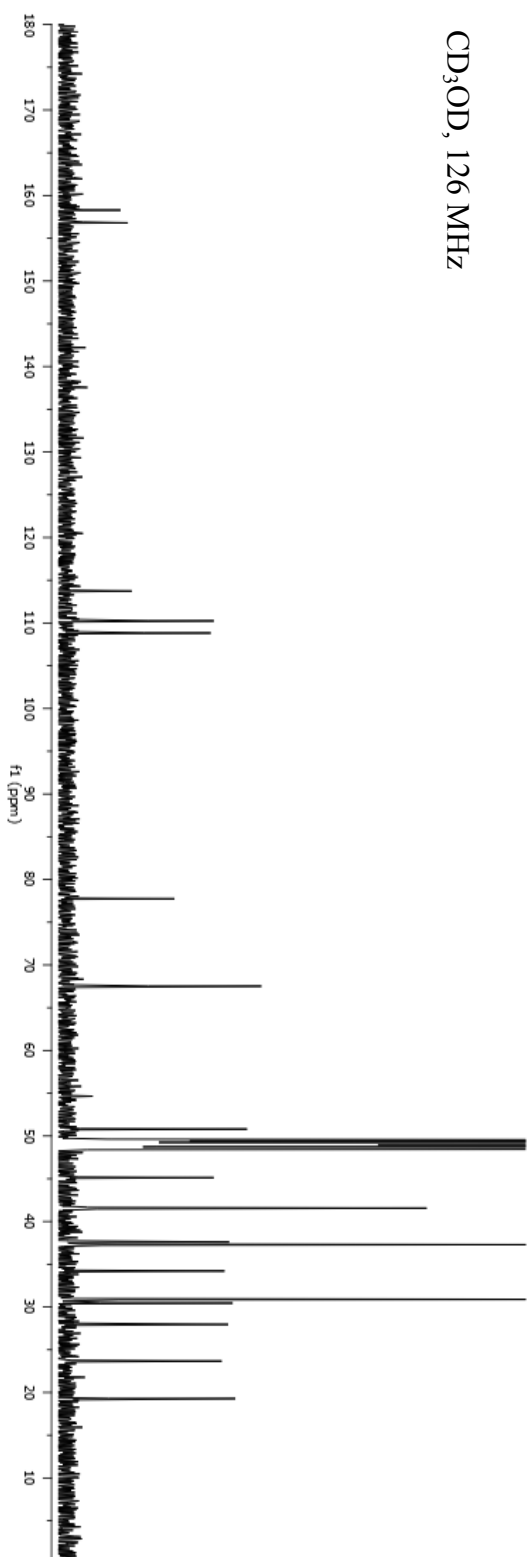
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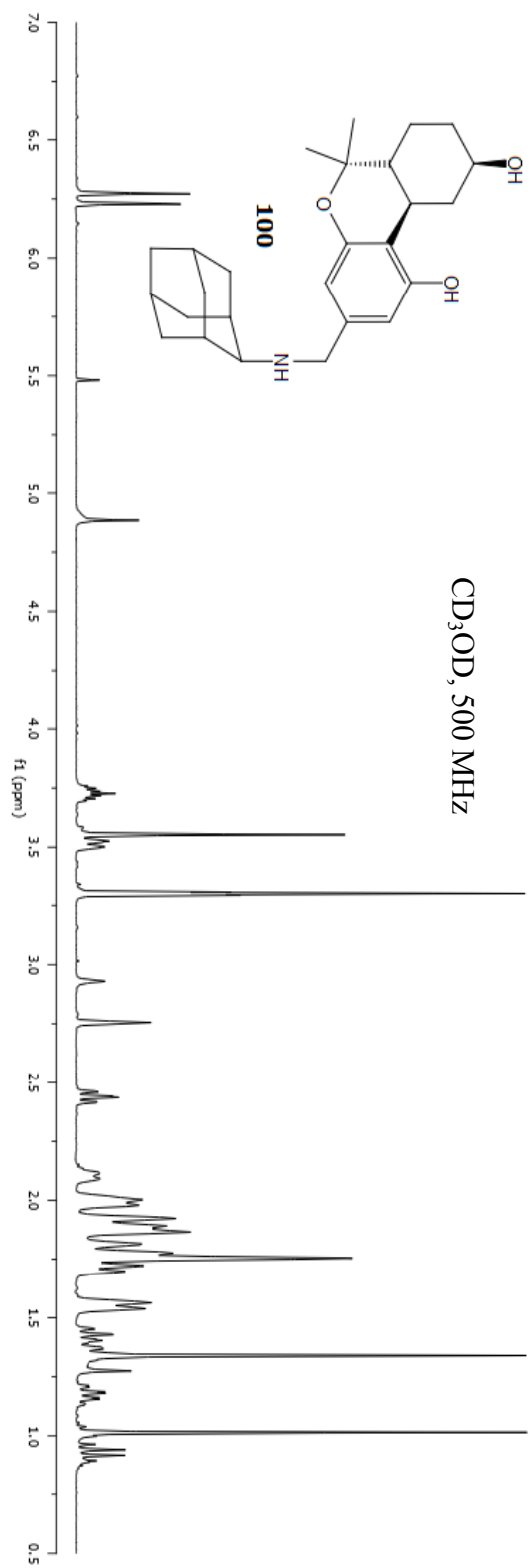




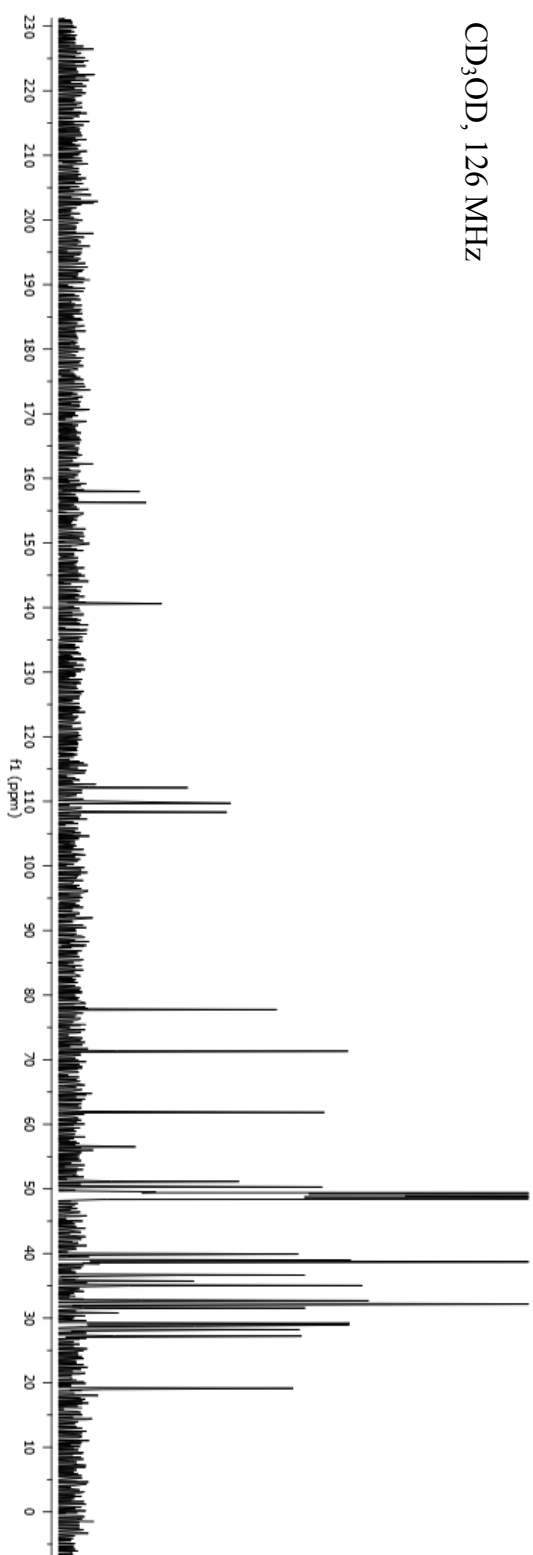


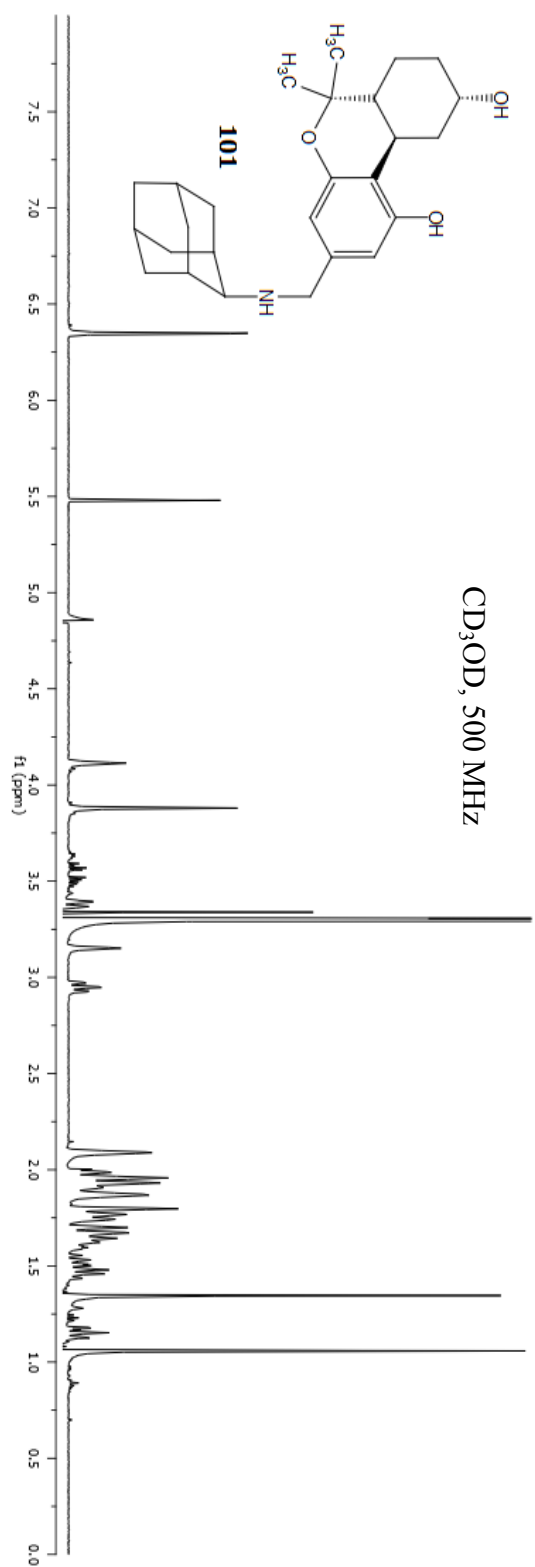
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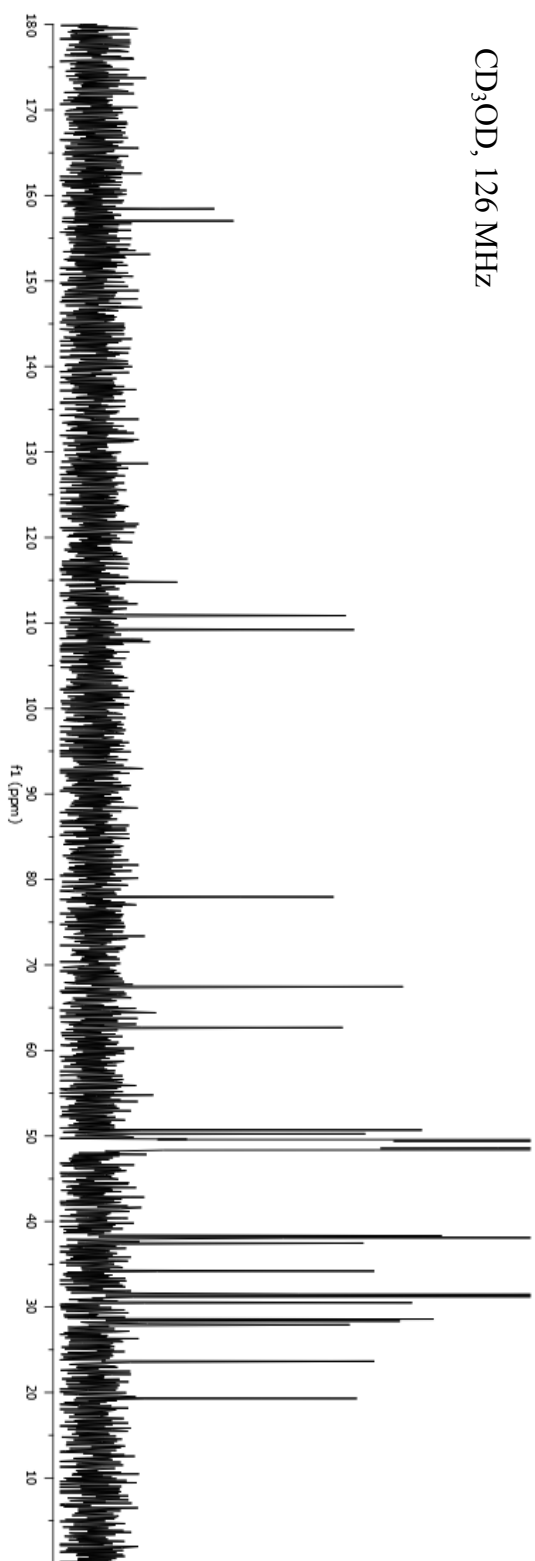


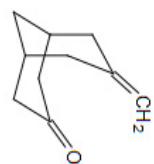
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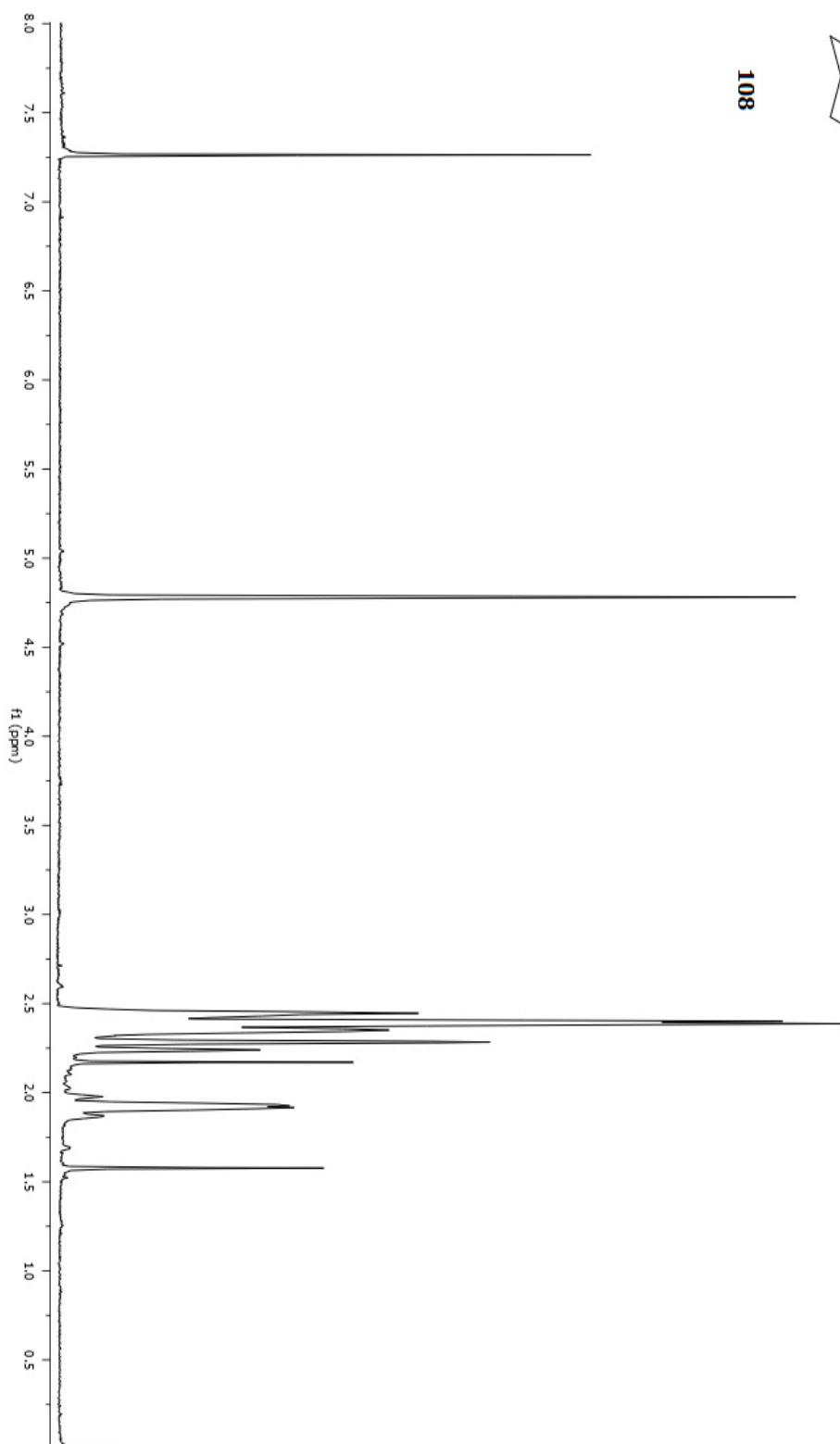
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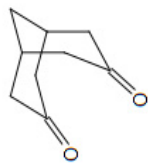




CDCl<sub>3</sub>, 300 MHz

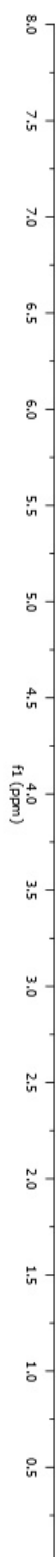
108

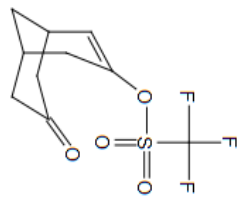




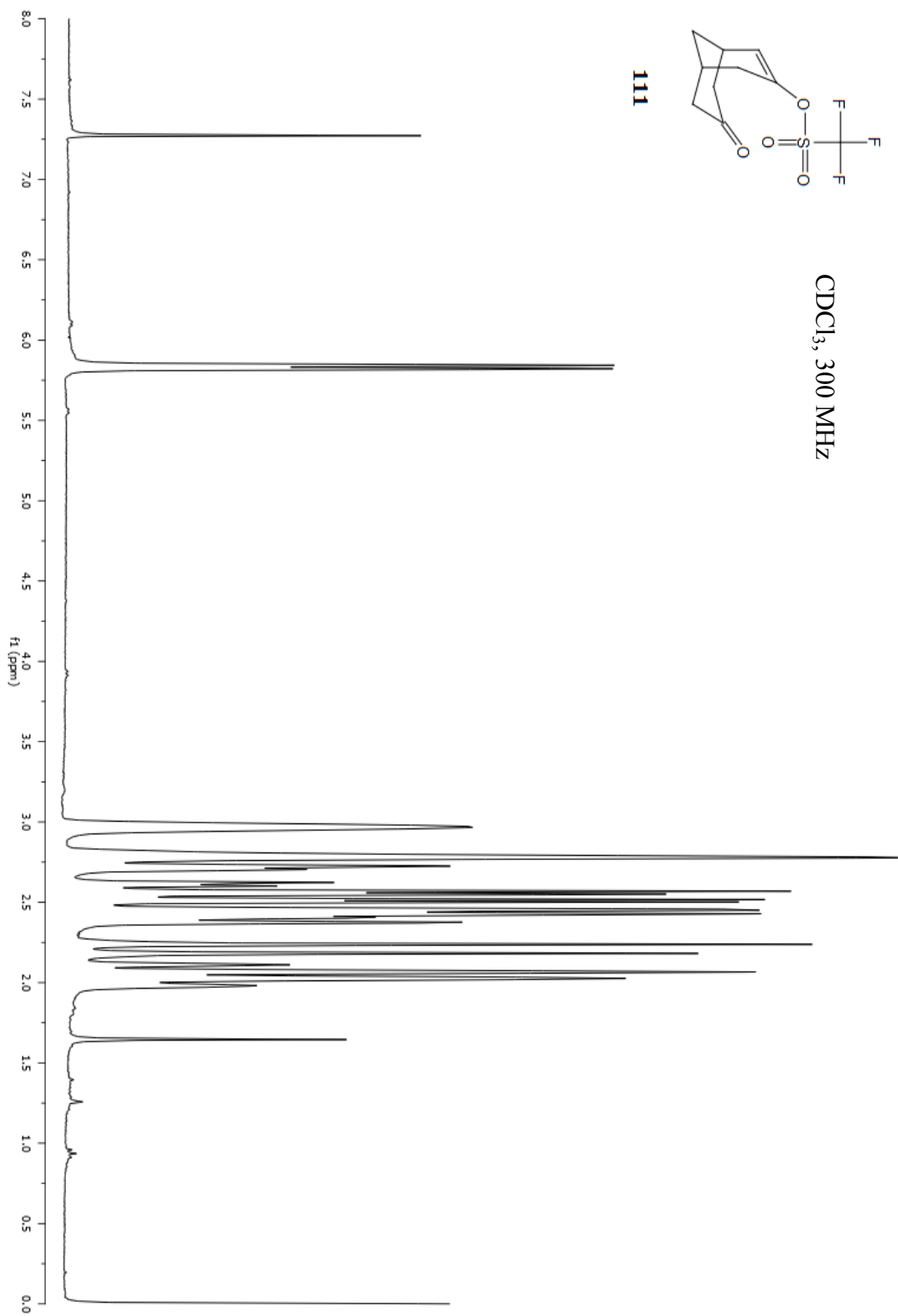
CDCl<sub>3</sub>, 300 MHz

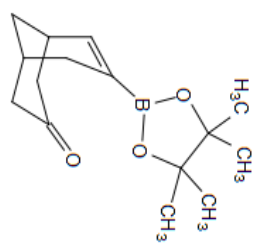
109



CDCl<sub>3</sub>, 300 MHz

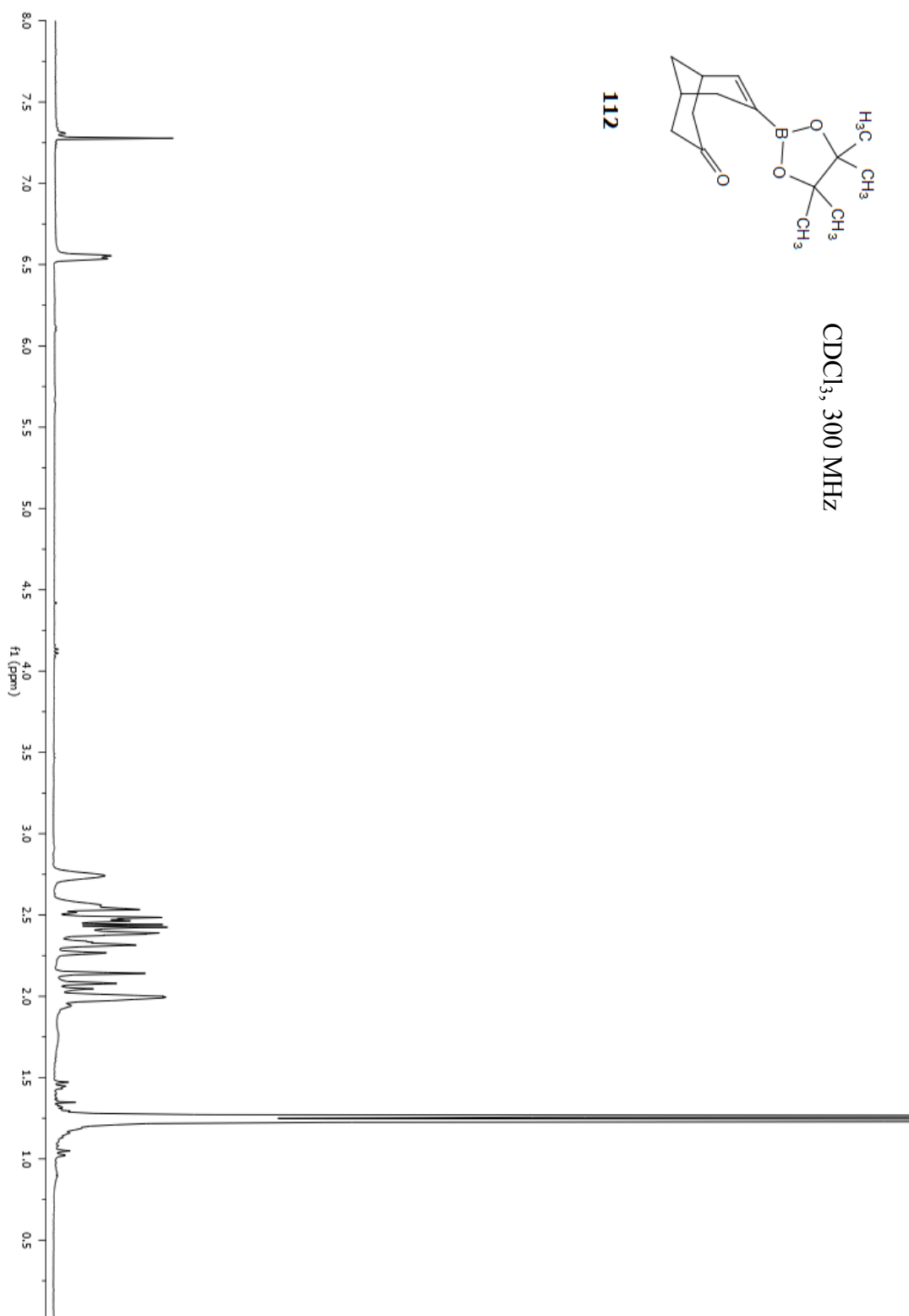
111

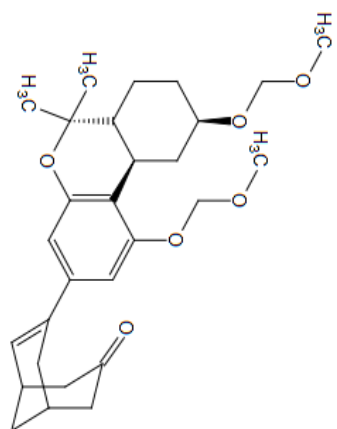




CDCl<sub>3</sub>, 300 MHz

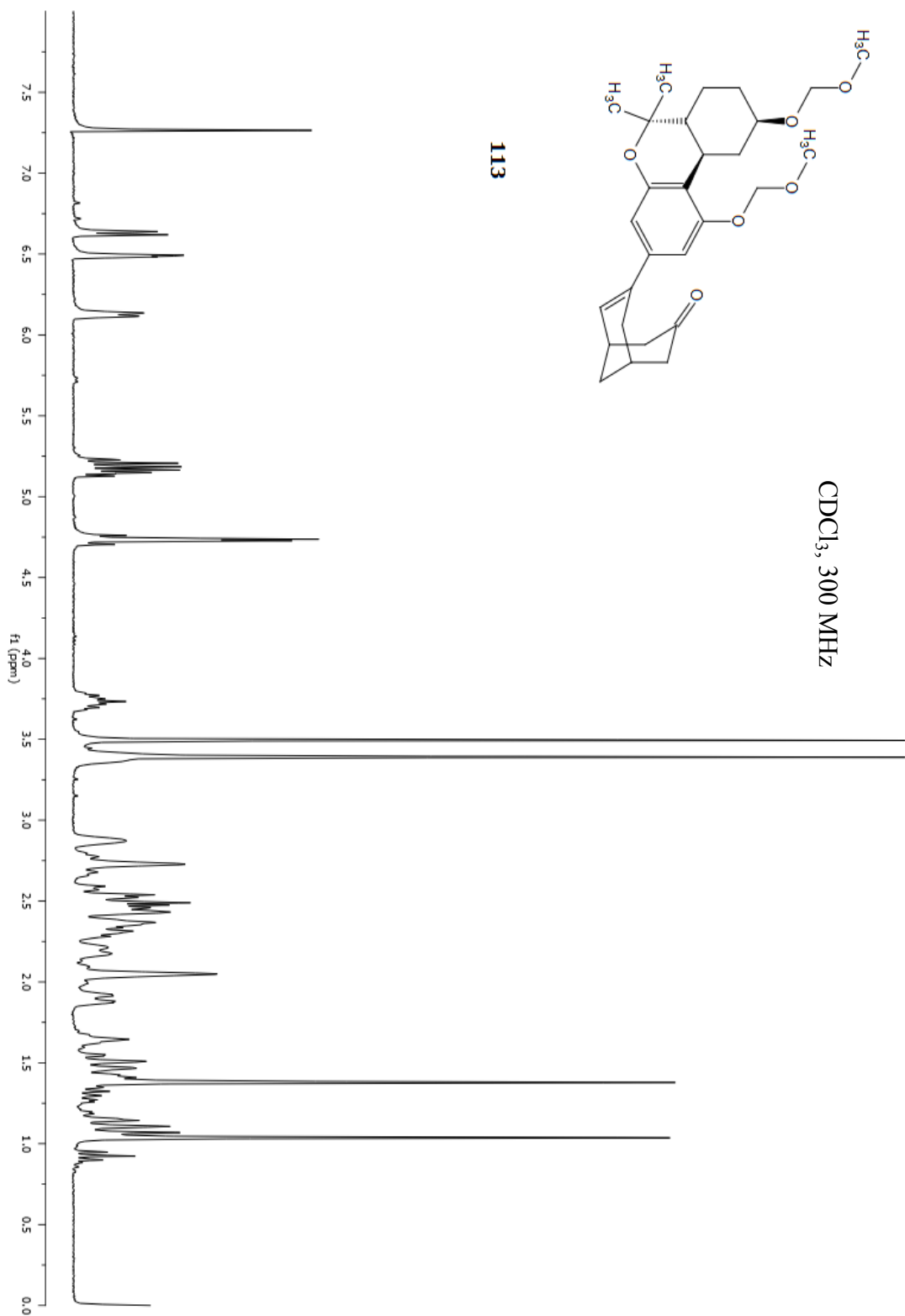
**112**



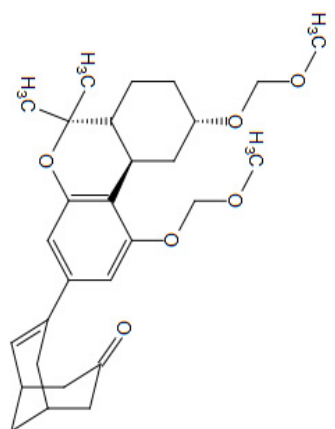


113

CDCl<sub>3</sub>, 300 MHz

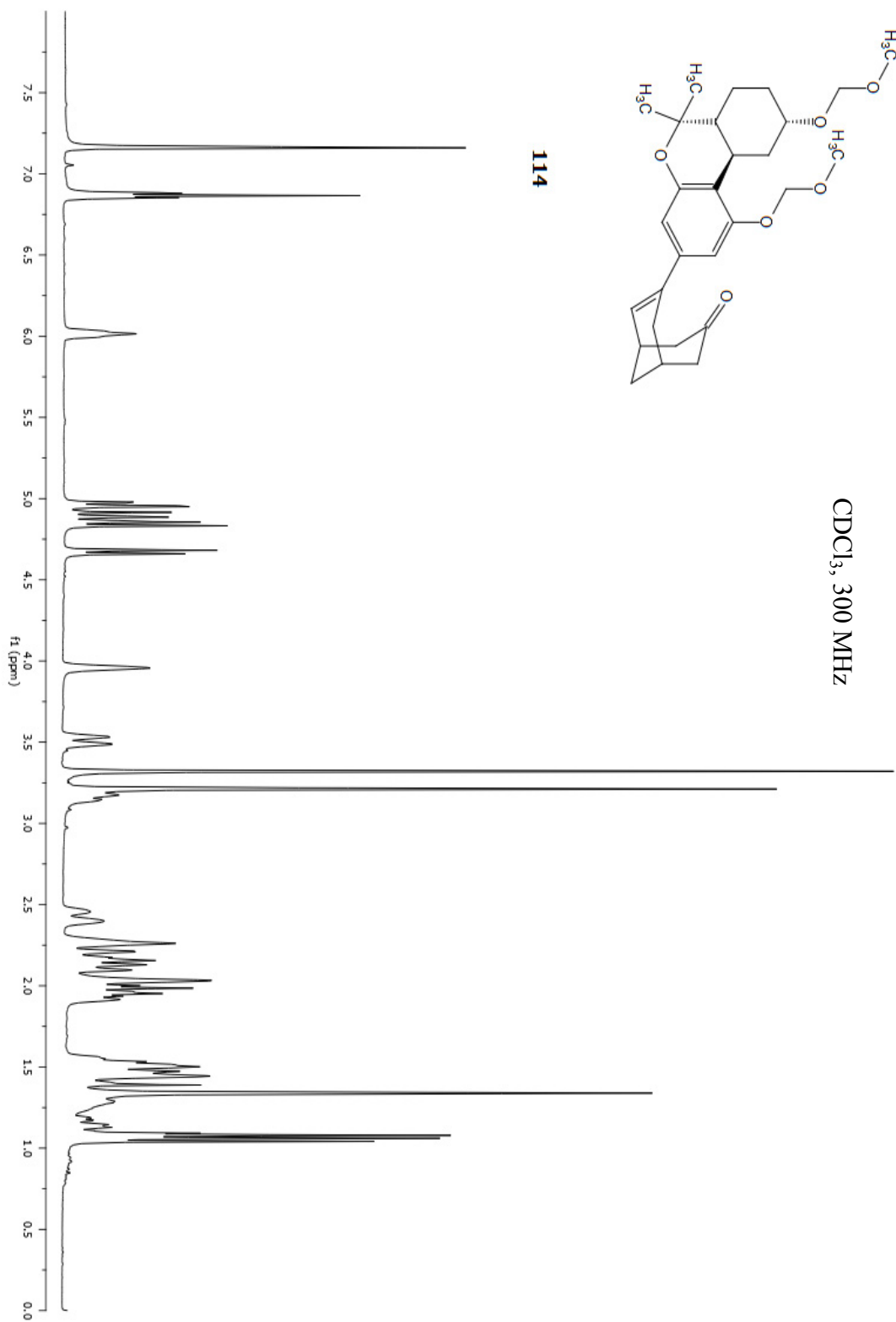


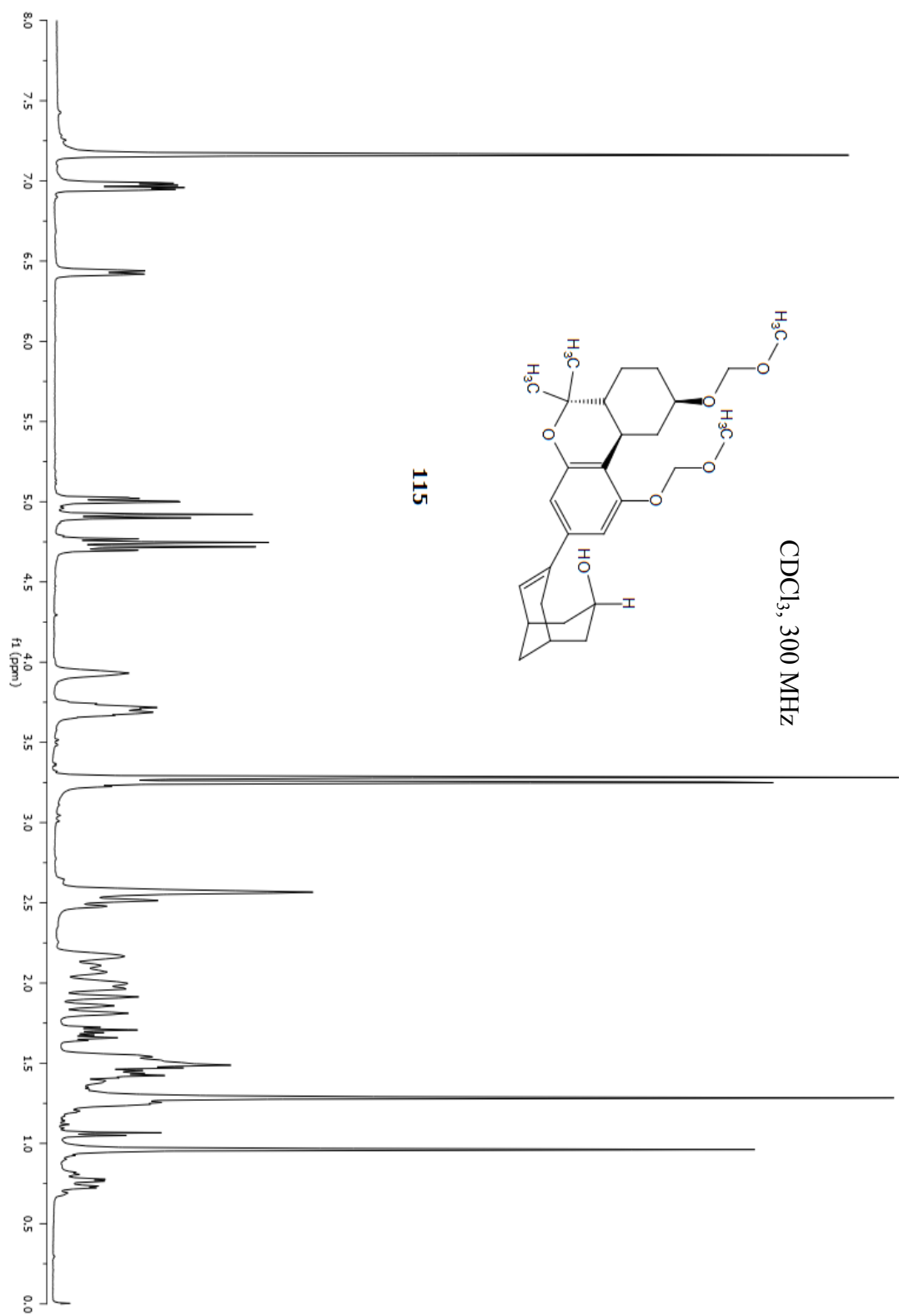




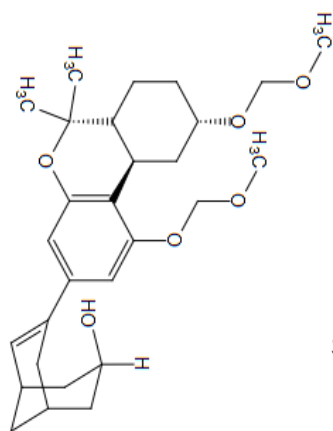
**114**

CDCl<sub>3</sub>, 300 MHz

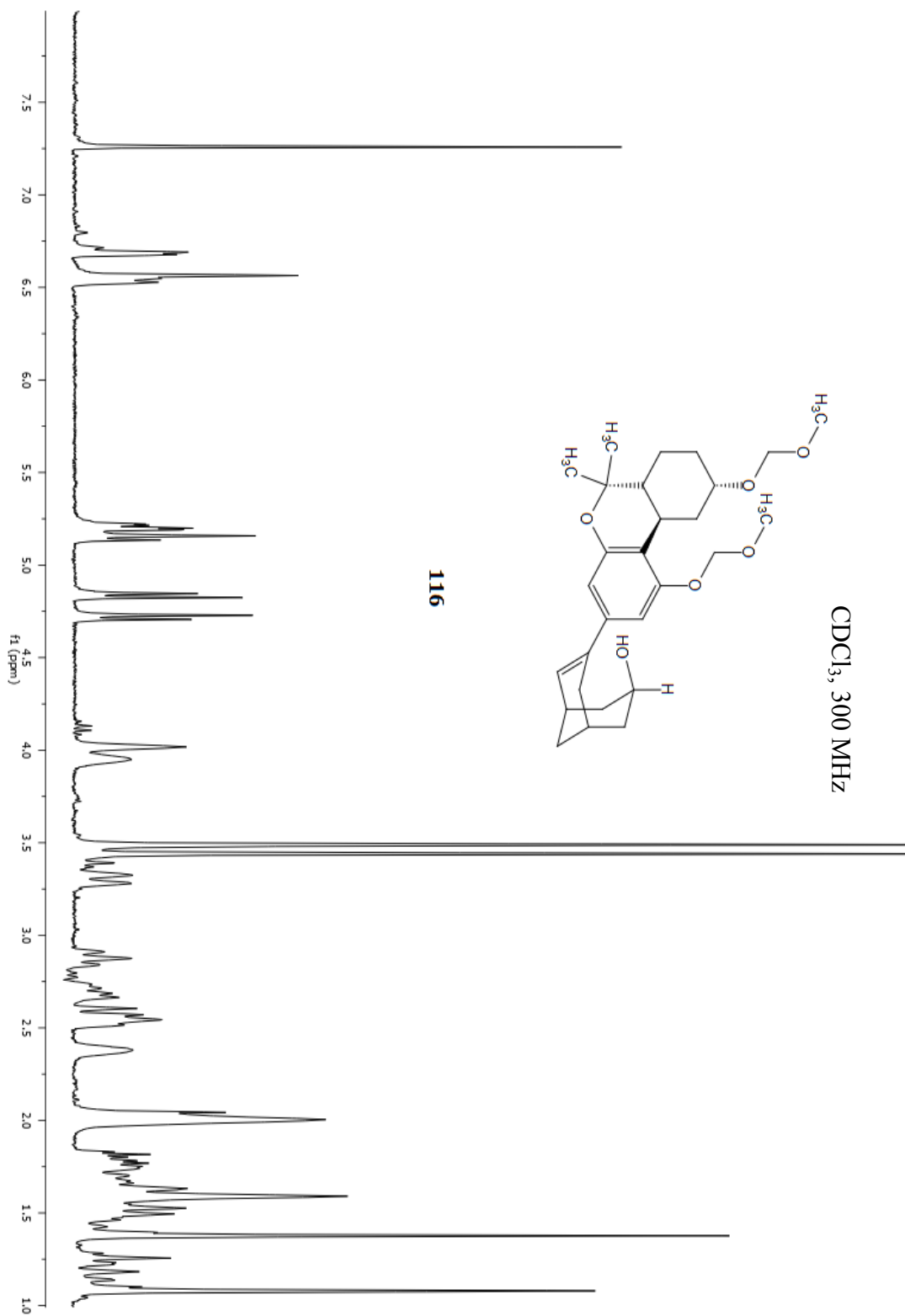




CDCl<sub>3</sub>, 300 MHz



116



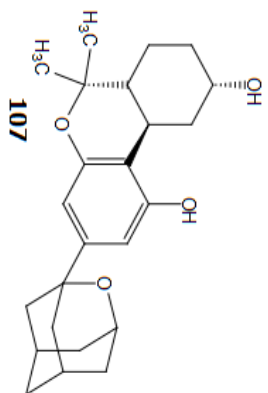
175

**106**

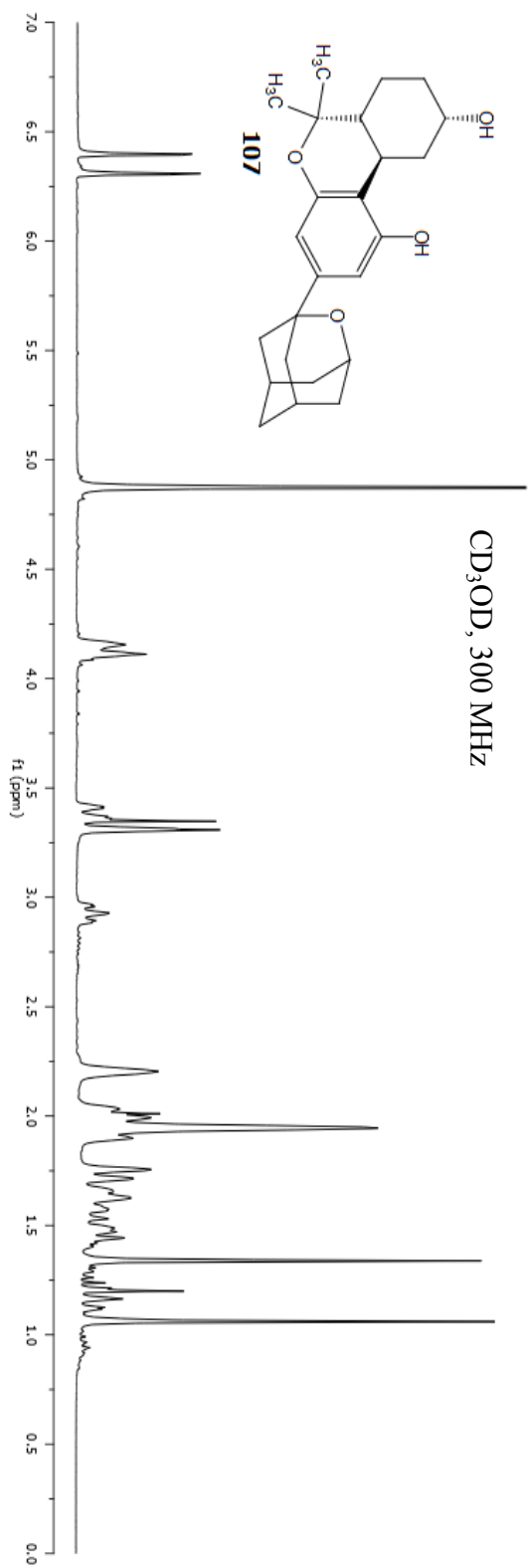
The chemical structure of compound 106 is a complex polycyclic molecule. It features a central benzene ring. Attached to the benzene ring is a spirocyclic ether system, specifically a spiro[3.5]non-2-ene derivative. Another substituent on the benzene ring is a side chain consisting of a methylene group, a chiral center with a methyl group (H<sub>3</sub>C) and a hydroxyl group (OH), and a terminal methyl group (H<sub>3</sub>C). The stereochemistry is indicated with wedges and dashes.



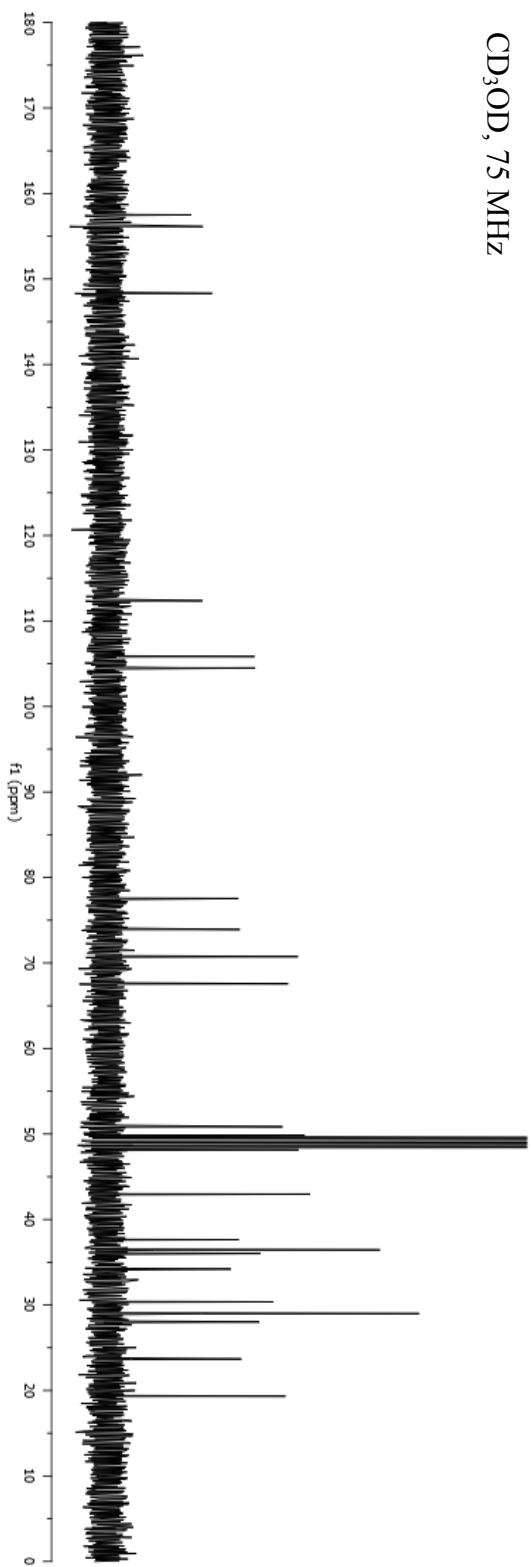
$C_6D_6$ , 126 MHz



CD<sub>3</sub>OD, 300 MHz



CD<sub>3</sub>OD, 75 MHz



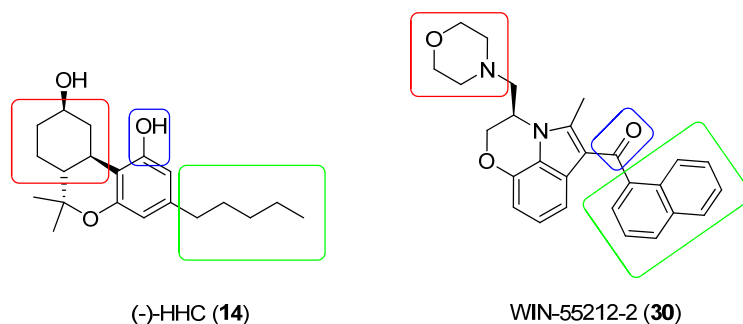
## **PART II**

### **THE SYNTHESIS OF C3 HETEROAROYL CANNABINOIDS**

## 6 Introduction

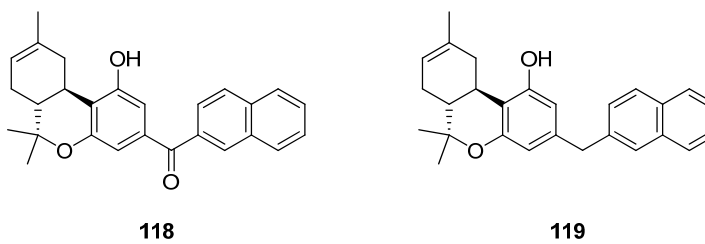
The goal of this project was to further investigate the pharmacophoric properties of the C3 substituent and to probe the spatial requirements of the two cannabinoid receptors. By installing a heteroaroyl group at C3 (**Figure 6.1** green box), we also hoped to discover important polar interactions between the ligand and key amino acids in the receptor. If a high affinity ligand were to be discovered, these C3 heteroaroyl cannabinoids could potentially be used as irreversible photoaffinity labels for the receptor(s) potentially resulting in discovery of the key amino acids that interact with the ligand in the active binding site as well as determining the orientation of the ligand within the active site.

The inspiration for this design was provided by our earlier studies of the structural homology between the aminoalkylindoles (e.g. WIN-55212-2, **30**) and classical cannabinoids (e.g. (-)-HHC, **14**).<sup>91</sup> Through the use of 2D NMR techniques and computational molecular modeling, it was suggested that the naphthoyl, morpholino and 3-keto groups of the aminoalkylindoles correspond to the C3 side chain, cyclohexyl ring and phenolic hydroxy of the classical cannabinoids, respectively (**Figure 6.1**).



**Figure 6.1** Structural homology between (-)-HHC (**14**) and WIN-55212-2 (**30**).

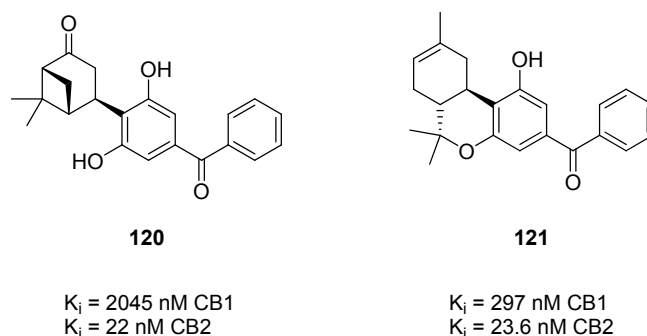
The synthesis of C3 naphthoyl and naphthylmethyl tricyclic cannabinoids (**118** and **119**), which were shown to be good ligands for CB1, supported this hypothesis (**Figure 6.2**).<sup>92</sup>



**Figure 6.2** Makriyannis' C3 naphthoyl and naphthylmethyl cannabinoids.

Recently, the Makriyannis group<sup>93</sup> has shown that bicyclic analogs with a benzoyl unit at C3 such as **120**, are selective for CB2 while Moore<sup>94</sup> has shown that the tricyclic  $\Delta^8$ -THC analog **121**, is also selective for CB2 (**Figure 6.3**)



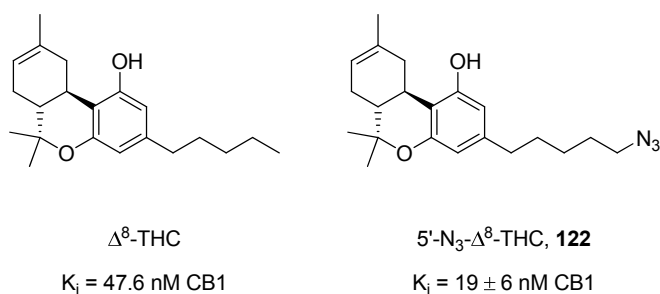


**Figure 6.3** CB2 selective C3 aryl cannabinoids.

### 6.1 Probes for the Cannabinoid Receptors

In order to gain new SAR information, molecular level interactions between the ligand and cannabinoid receptor(s) have been studied using covalent probes. A 3D model<sup>95</sup> of the CB1 receptor has been constructed based on the comparison of the amino acid sequence of numerous other GPCR's whose structure is known in greater detail. Based on these comparisons, the receptor was predicted to consist of seven linked  $\alpha$ -helices and their relative positions were calculated using an array of molecular modeling techniques. The proposed helix bundle resembles that of the G-protein coupled visual pigment, rhodopsin, whose structure is known from a 2.8 Å resolution crystal structure.<sup>96</sup> In order to determine the structure and location of the binding site(s), experiments with irreversible covalent probes have been conducted.

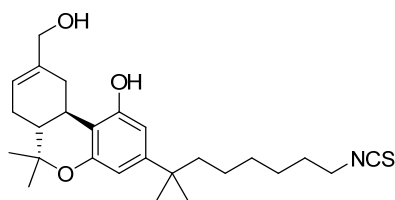
The first such photoaffinity label, 5'-N<sub>3</sub>- $\Delta^8$ -THC (**122**), was prepared by the Makriyannis group in 1992 (**Figure 6.1.1**).<sup>97</sup> Binding experiments revealed that **122** has a two-fold increase in affinity for CB1 when compared to  $\Delta^8$ -THC. In order to test the ability



**Figure 6.1.1** The first CB1 selective photoaffinity label **122**.

of **122** to inactivate the CB1 receptor, photoirradiation experiments were conducted. Rat forebrains were saturated with **122** to ensure receptor occupancy was greater than 98% and then irradiated with shortwave ultraviolet light. After irradiation was complete, the membranes were washed extensively to remove any unbound **122** and then retested for cannabinoid binding. The membrane that was equilibrated with **122** and irradiated resulted in no specific binding of [ $^3\text{H}$ ]-CP-55,940. It should also be noted that exposure of the membrane preparations to ultraviolet light did not result in any damage to the membranes as irradiated control membranes did not exhibit reduced binding affinity.

In 1994, the Makriyannis group reported (-)-11-hydroxy-7'-isothiocyanato-1',1'-dimethylheptyl- $\Delta^8$ -THC (**123**) as the first irreversible covalent probe for the CB1 receptor (**Figure 6.1.2**).<sup>98</sup> The isothiocyanate group was chosen because it is inert to neutral water but capable of nucleophilic reactions with amino, hydroxyl and sulfhydryl groups under physiological conditions.<sup>99</sup> Also, isothiocyanate containing ligands have been used for the study and characterization of a series of receptors including the opioid,<sup>100, 101</sup> NMDA,<sup>102</sup>  $\sigma$ <sup>103</sup> and benzodiazepine<sup>104</sup> receptors.



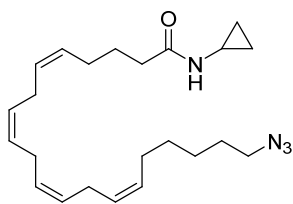
**123**

$K_i^* = 3.2 \text{ nM CB1}$

**Figure 6.1.2** CB1 selective high affinity covalent probe **123**.

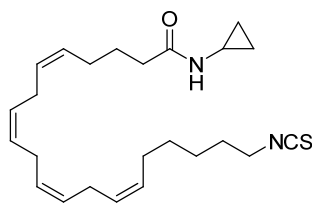
Rat forebrain membranes were used to assess the binding affinity of **123** via a filtration assay using [ $^3\text{H}$ ]-CP-55,940 as the radioligand resulting in an apparent  $K_i$  of 3.2 nM. Because the ligands undergo irreversible binding the apparent  $K_i$  must be reported. The ligand (**123**) was then evaluated for its ability to irreversibly label the receptor by treating rat forebrain membranes with varying amounts of the ligand. When a large amount (over ten times its apparent  $\text{IC}_{50}$ ) of **123** was used, complete labeling of the receptor was achieved after five minutes of incubation, indicating a rapid reaction between the ligand and receptor. The success of these experiments clearly showed that high-affinity classical cannabinoid ligands can covalently attach themselves to the active site of the receptor and also suggested that there is a thiol, amino or hydroxyl amino acid residue at or in the vicinity of the active binding site of the receptor.

The first two high affinity covalent anandamide probes for the CB1 receptor (**Figure 6.1.3**) were also recently prepared by the Makriyannis group.<sup>105</sup> To impart optimal CB1 affinity the headgroup of the anandamide analogs contained a cyclopropyl substituent.<sup>106</sup>



AM-3661, **124**

$K_i = 0.9 \text{ nM CB1}$   
 $K_i = 57.6 \text{ nM CB2}$

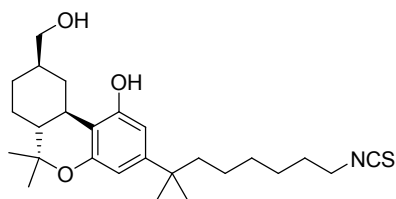


AM-3677, **125**

$K_i^* = 1.3 \text{ nM CB1}$   
 $K_i^* = 48.5 \text{ nM CB2}$

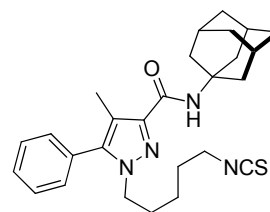
**Figure 6.1.3** High affinity covalent anandamide probes.

Until recently, a high affinity covalent probe for the CB2 receptor had not been developed. The Makriyannis group recently published results on two such compounds (**126** and **127**) (**Figure 6.4**).<sup>107, 108</sup>



AM-841, **126**

$K_i^* = 1.5 \text{ nM CB2}$

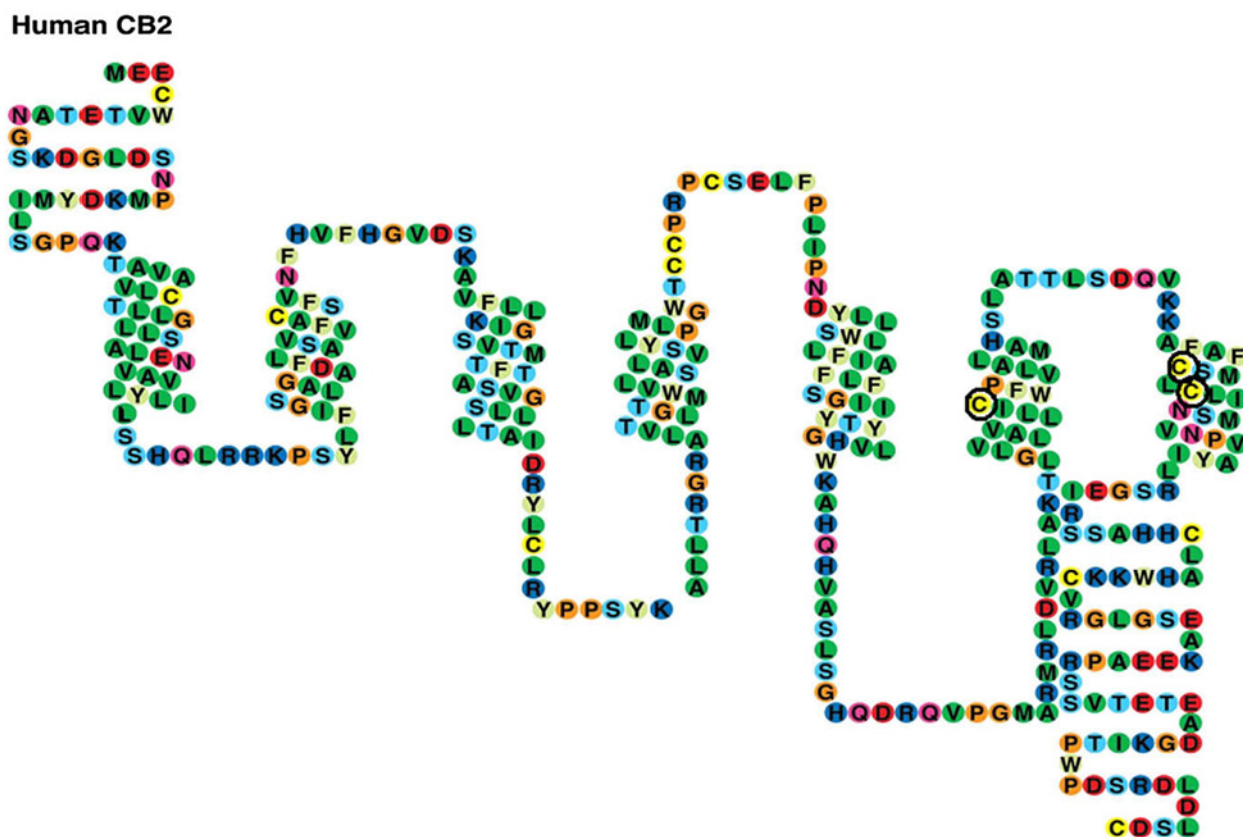


AM-1336, **127**

$K_i^* = 0.54 \text{ nM CB2}$

**Figure 6.1.4** High affinity CB2 selective covalent probes.

The first compound, **126**, is based on the classical cannabinoid tricyclic framework. Through the use of LAPS and site directed mutagenesis, the Makriyannis group were able to determine that cysteine residue, C6.47(257) residing in transmembrane helix six, is the site of covalent attachment in the receptor that leads to activation (**Figure 6.1.5**).

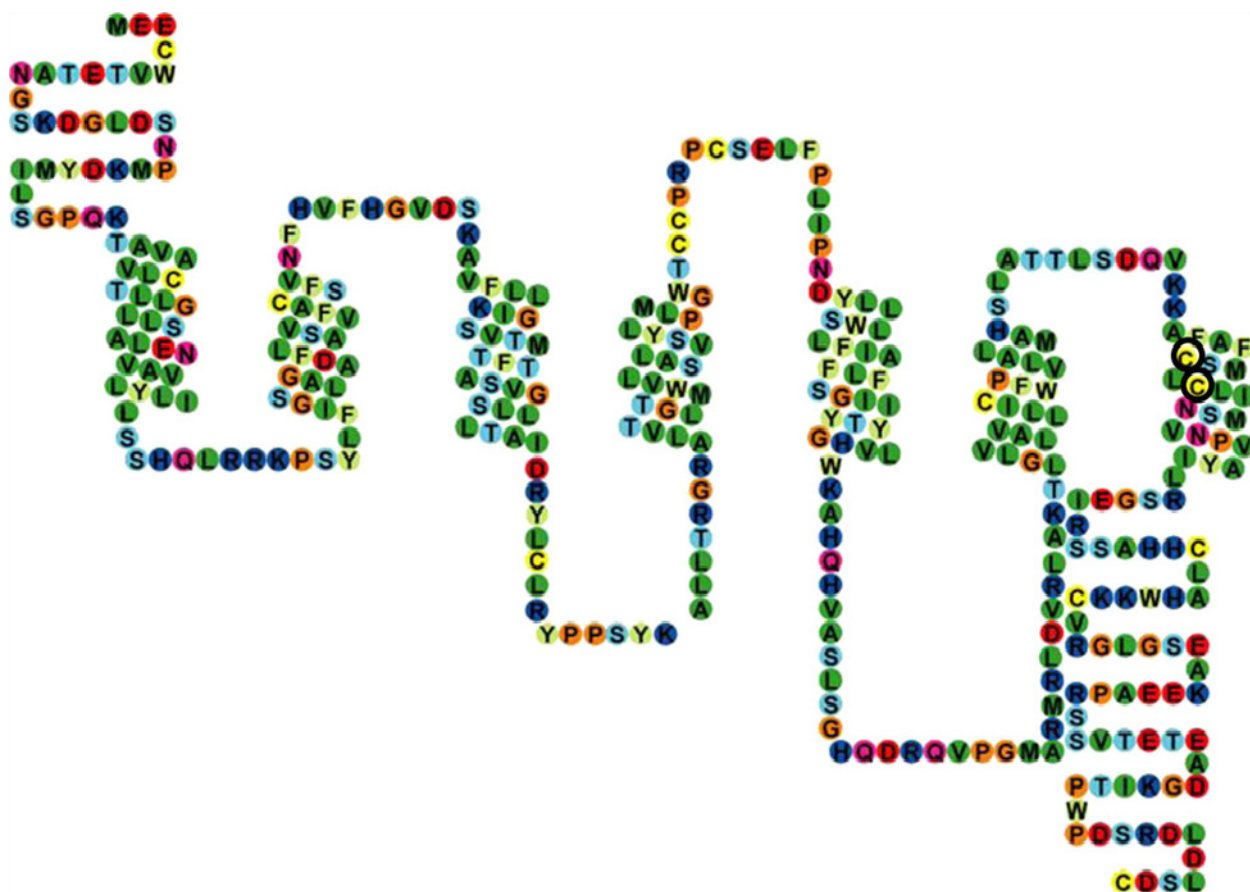


**Figure 6.1.5** Schematic representation of the human CB2 receptor. Amino acids subjected to mutation, C6.47(257), C7.38(248) and C7.42(288) are circled in bold.<sup>107</sup>

Of the five cysteine residues modeled in the ligand-binding pocket of the human CB2 receptor, C6.47(257) is located most deeply within the pocket, near the center of the lipid bilayer.<sup>109</sup> On the assumption that the NCS functional group of AM-841 reacts with the first cysteine residue with which it comes into contact in the human CB2 receptor's ligand-binding pocket, identification of C6.47(257) as the site for covalent attachment of AM-841 to the human CB2 receptor suggests that the tail of AM-841 enters the receptor's binding pocket at great depth.

Diarylpyrazole **127** was also studied using LAPS and site directed mutagenesis.

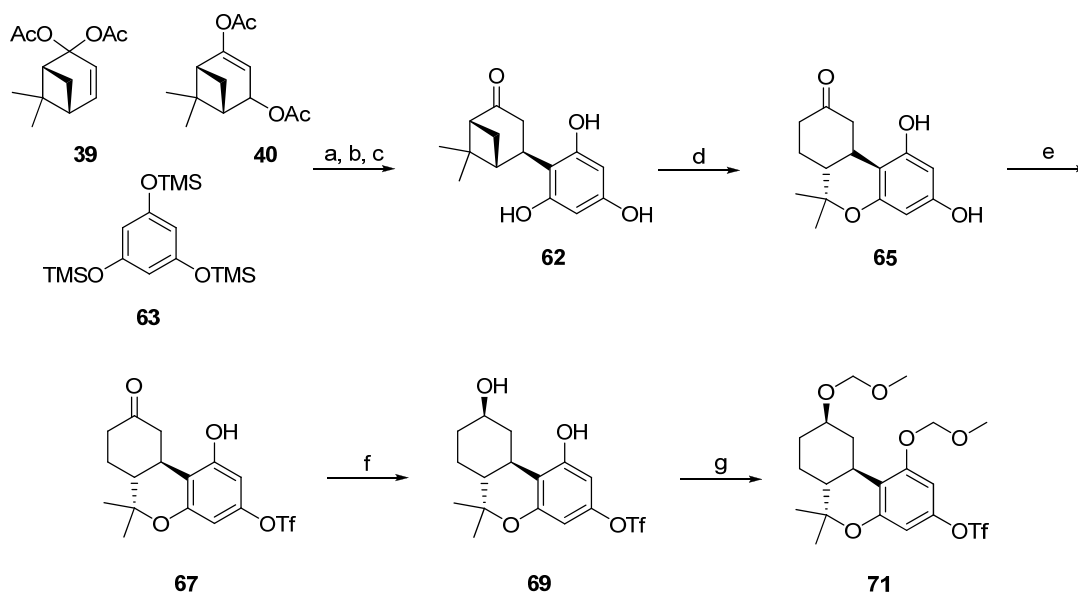
Experiments involving mutant CB2 receptors revealed that the 1,5-diarylpyrazole class of compounds interact with a different cysteine residue when compared to the classical cannabinoids. Cysteine residues C7.38(284) and C7.42(288) in transmembrane helix seven were shown to be critical for optimal binding interaction and ligand recognition (Figure 6.1.6).



**Figure 6.1.6** Schematic representation of the human CB2 receptor. The key amino acids critical for optimal binding and ligand recognition, C7.38(284) and C7.42(288), are circled in bold.<sup>108</sup>

## 7 Chemistry

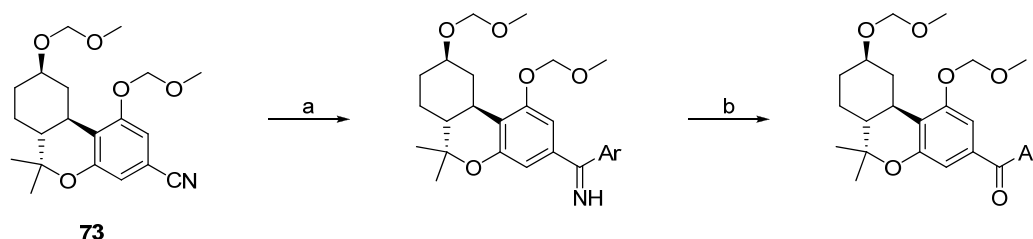
With our recent success in the synthesis of C3 heteroadamantyl cannabinoids,<sup>110</sup> we chose to utilize the same approach to synthesize C3 heteroaroyl analogs preparing all compounds from an advanced intermediate such as **71** (**Scheme 7.1**). Only the C9  $\beta$ -hydroxy series were of interest since they typically show enhanced binding affinity compared to their C9  $\alpha$ -hydroxy counterparts.



**Scheme 7.1** Reagents and conditions: (a) TsOH·H<sub>2</sub>O, 4/1 CHCl<sub>3</sub>/acetone, 0 °C to rt; (b) Ac<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>, DMAP (cat.), pyridine, 0 °C to rt; (c) KOH, MeOH, 0 °C; 68% overall from **39** and **40**; (d) TMSOTf, MeNO<sub>2</sub>, 0 °C; (e) PhNTf<sub>2</sub>, NEt<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt; 57% from **62**; (f) NaBH<sub>4</sub>, MeOH, 0 °C; 97% **69** + **70**, ca. 95/5; (g) MeOCH<sub>2</sub>Cl, (*i*-Pr)<sub>2</sub>NEt, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 2.5 h; 93%.

Initially, we envisioned the efficient conversion of aryl triflate **71** to nitrile **73** followed by addition of aryl Grignard reagents and subsequent hydrolysis leading to the desired phenones (**Scheme 7.2**). To our surprise, we did not observe any of the desired phenone

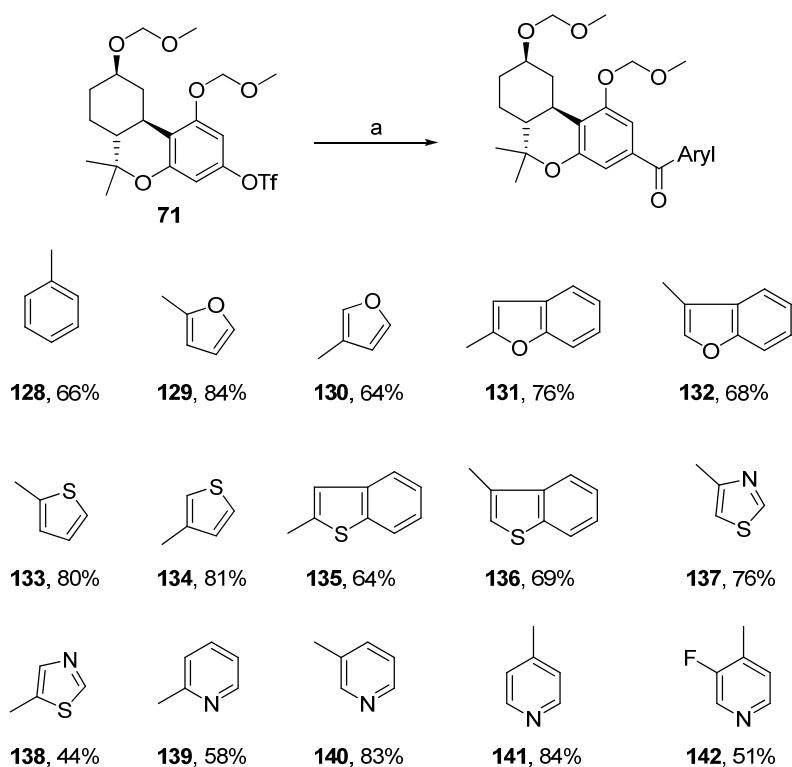
when nitrile **73** was treated with excess aryl Grignard reagent. Instead, only recovered starting material was obtained. We believe this can be attributed to the decreased nucleophilicity of aryl magnesium reagents and nitrile **73** being a poor electrophile.



**Scheme 7.2** Reagents and conditions: (a) THF, ArLi or ArMgBr, Reflux, additives; (b)  $\text{H}_3\text{O}^+$ .

To circumvent this problem, we sought to exploit the aryl triflate **71** by using a carbonylative Stille process. This approach was very attractive since it increased the overall efficiency of the synthesis and a wide variety of heteroaryl stannanes are commercially available or easily prepared from their respective aryl bromides or iodides. Exposure of triflate **71** to a slight excess of heteroaryl stannane, LiCl, 4 Å molecular sieves, BHT, and catalytic  $\text{PdCl}_2(\text{dppf}) \cdot \text{CH}_2\text{Cl}_2$  in DMF at 110 °C under an atmosphere of CO for 24 h led to protected heteroaryl cannabinoids **128 - 142** in moderate to excellent yields (**Scheme 7.3**) It should be noted that under these reaction conditions none of the direct coupling of triflate with stannane was observed.

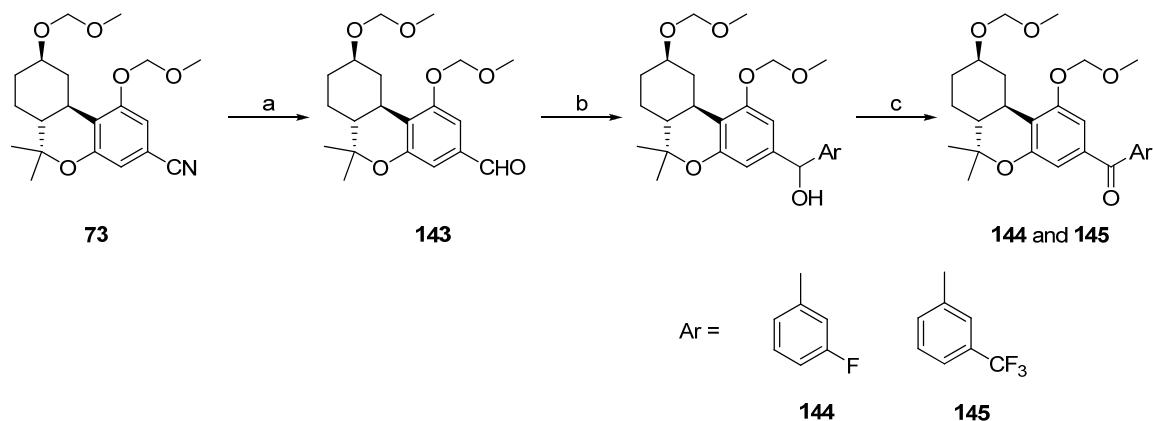




**Scheme 7.3** Reagents and conditions: (a) DMF, CO, LiCl, BHT, 4Å MS, 110 °C, ArSnBu<sub>3</sub>, PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub>, 24 h.

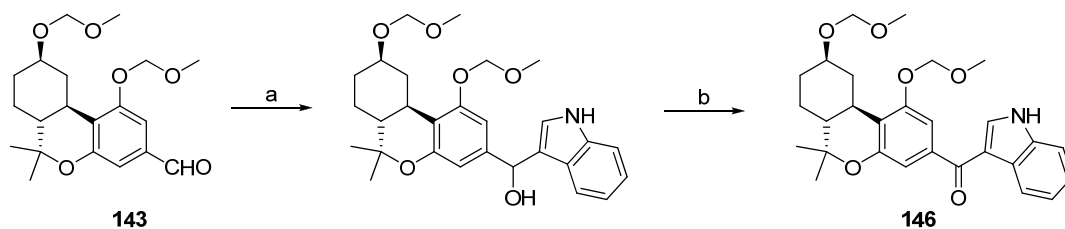
In cases in which the aryl stannane was either not commercially available or unreactive, a slightly modified synthetic procedure was used in order to prepare the heteroaroyl compounds. Since we had shown nitrile **73** to be unreactive towards aryl Grignard reagents, we believed that a two step process involving nucleophilic addition of aryl lithium reagents to aldehyde **143** and subsequent oxidation would yield the desired phenones. Reduction of nitrile **73** to aldehyde **143** with DIBAL took place in 96% yield. Nucleophilic addition of aryl lithium reagents derived from 3-bromofluorobenzene and 3-bromobenzotrifluoride to **143** followed by oxidation of the respective benzylic alcohols with manganese oxide led to phenones **144** and **145** in 74% and 81% yield, respectively

(**Scheme 7.4**). Oxidation of the benzylic alcohols with Dess-Martin periodinane (DMP) was also attempted but none of the desired phenone product was observed.



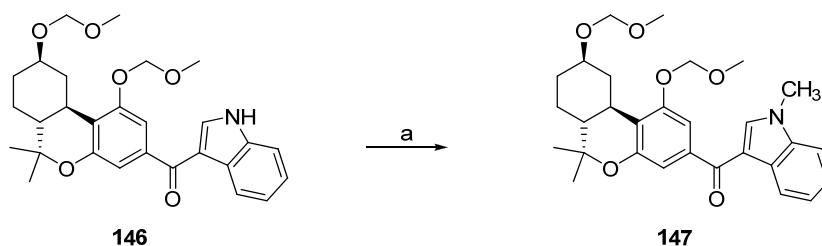
**Scheme 7.4** Reagents and conditions: (a)  $\text{CH}_2\text{Cl}_2$ , DIBAL,  $-78^\circ\text{C}$ ; 96%; (b) ArBr, *n*-BuLi, THF,  $-78^\circ\text{C}$ ; (c)  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ ; **144**, 74% from **143**; **145**, 81% from **143**.

Exposure of **143** to indole in methanolic KOH followed by oxidation with manganese dioxide led to **146** in 52% yield over the two steps (**Scheme 7.5**).



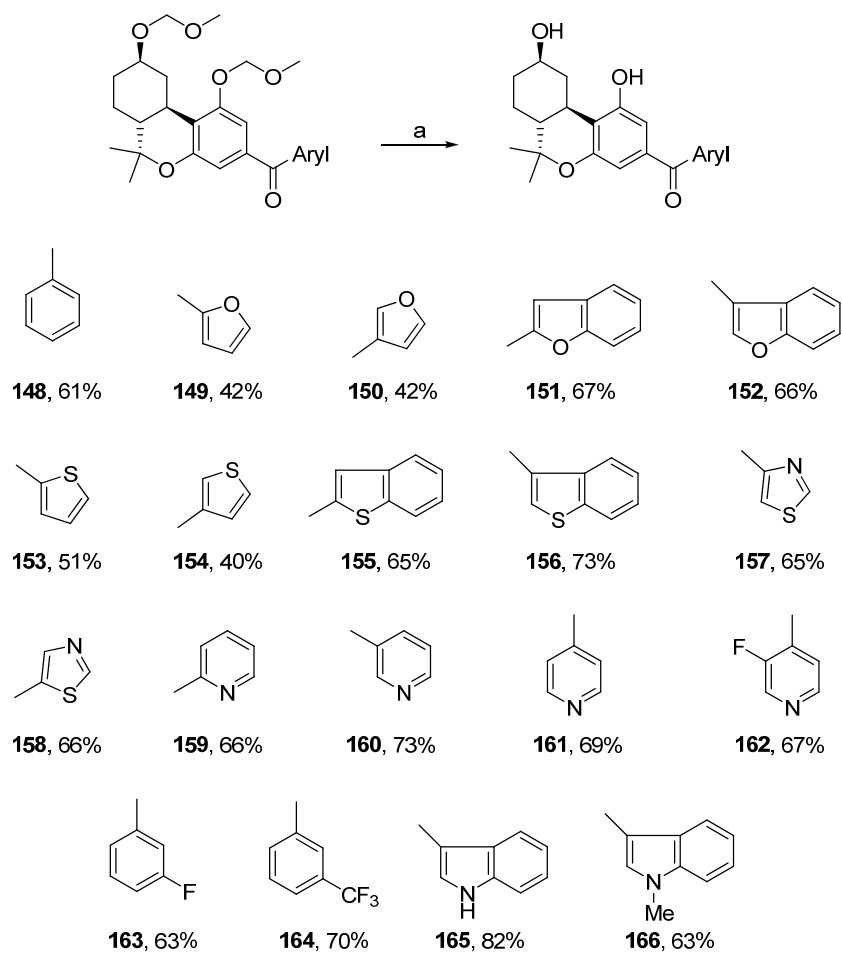
**Scheme 7.5** Reagents and conditions: (a) KOH, MeOH, indole; (e)  $\text{MnO}_2$ ,  $\text{CH}_2\text{Cl}_2$ ; 52% from **143**.

Treatment of indole **146** with NaH and iodomethane in DMF furnished the *N*-methylated compound **147** in 97% yield (**Scheme 7.6**).



**Scheme 7.6** Reagents and conditions: (a) DMF, NaH, MeI; 97%.

Once again, removal of the methoxymethyl ether protecting groups proved to be slightly problematic. Treatment of protected phenones **128 - 142** and **144 - 147** with TMSBr in  $\text{CH}_2\text{Cl}_2$  at  $-40\text{ }^\circ\text{C}$  for 1.5 h and then  $0\text{ }^\circ\text{C}$  for 1 h led to diols **148 - 166** in moderate to good yields (**Scheme 7.7**). The low yield for deprotection of the furyl and thiophenyl compounds can be attributed to the high nucleophilicity of the electron rich aromatic ring. Reaction with the methoxymethyl bromide that is generated under these reaction conditions may be responsible for the appearance of byproducts. Low yields were also observed in the presence of the acid scavenger poly(4-vinylpyridine), which rules out that the low yields of the deprotected products are due to the presence of strong acid. Other common conditions to remove methoxymethyl ethers such as methanolic HCl or  $\text{ZnBr}_2/n\text{-BuSH}$ , which served us well in the past, also failed to improve the yields.



**Scheme 7.7** Reagents and conditions: (a) TMSBr, CH<sub>2</sub>Cl<sub>2</sub>, -40 °C, 1.5 h; 0 °C, 1 h.

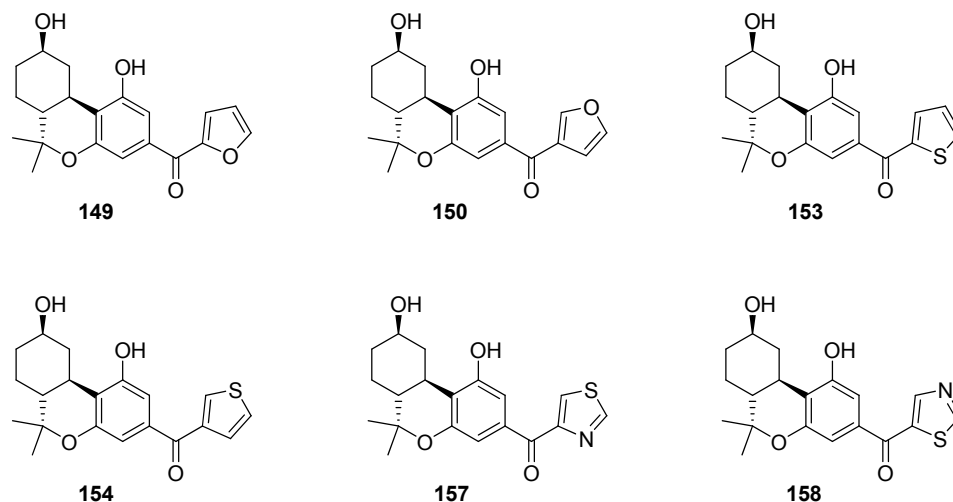
## 8 Receptor Binding Studies

Receptor binding studies of all final compounds were conducted at Northeastern University, Center for Drug Discovery under the direction of Professor Alexandros Makryiannis. Competitive binding assays with the radioligand [ $^3\text{H}$ ]-CP-55,940 (**3**) were carried out using rat brain or membranes from HEK293 cells to assess the affinities for CB1 and CB2 receptor binding sites, respectively, following previously described procedures. A series of experiments were conducted for each compound at varying concentrations and the results of which will be discussed in detail in this chapter. All compounds that showed binding affinities of greater than 1000 nM from the two point data experiments (run in triplicate) were not subjected to the human CB2 assay. Compounds having binding affinities of less than 1000 nM from the two point data experiments (run in triplicate) were subjected to eight point data experiments (run in triplicate) and were also subjected to the human CB2 assay.

Studies from the Makryiannis lab<sup>93</sup> have shown that bicyclic analog **120** containing a C3 benzoyl substituent exhibited high affinity for the human CB2 receptor (22 nM) with significant selectivity over the CB1 receptor (93 fold). The Moore lab<sup>94</sup> has reported tetrahydrocannabinol analog **121** with a C3 benzoyl substituent to be a high affinity CB2 selective ligand with moderate selectivity (12.6 fold). The presence of the 1'-keto functionality seems to impart selectivity for the CB2 receptor. However, further SAR data needed to improve the pharmacological profile of these cannabinoid analogs are lacking. To probe the stereoelectronic requirements of the C3 side chain and

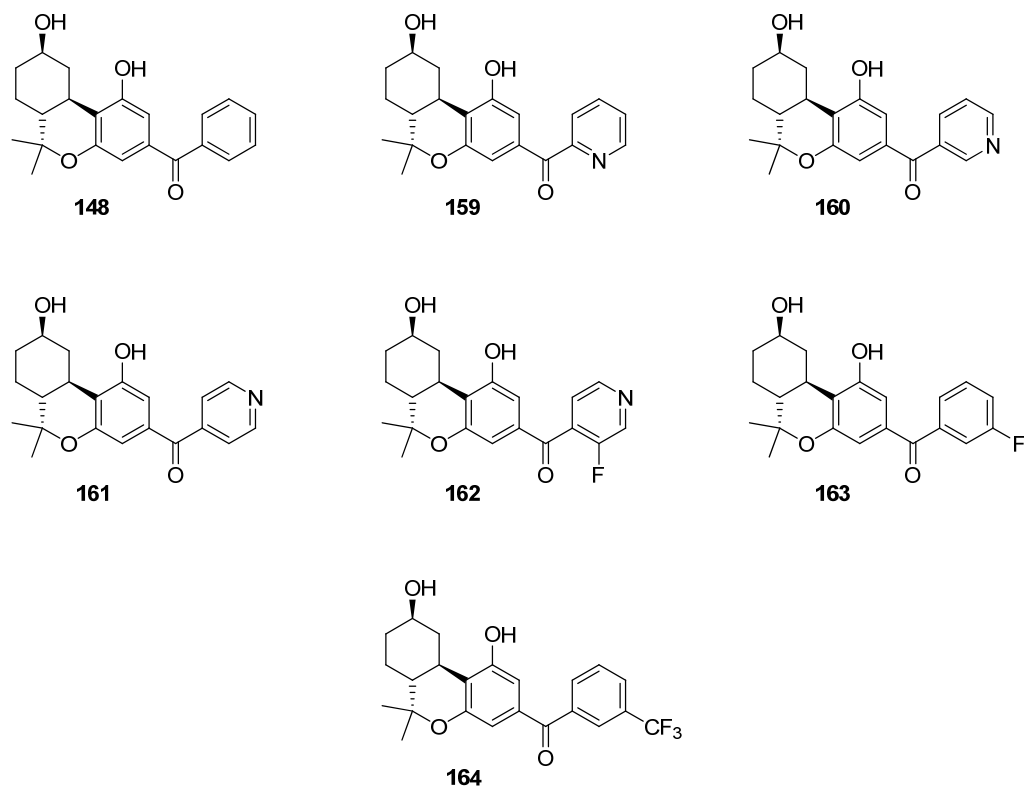
simultaneously improve the polar properties, three groups of C3 heteroaroyl compounds were designed and synthesized.

The first group includes analogs containing a five membered heteroaromatic ring appended to C3 through a carbonyl linker (**149**, **150**, **153**, **154**, **157** and **158**).



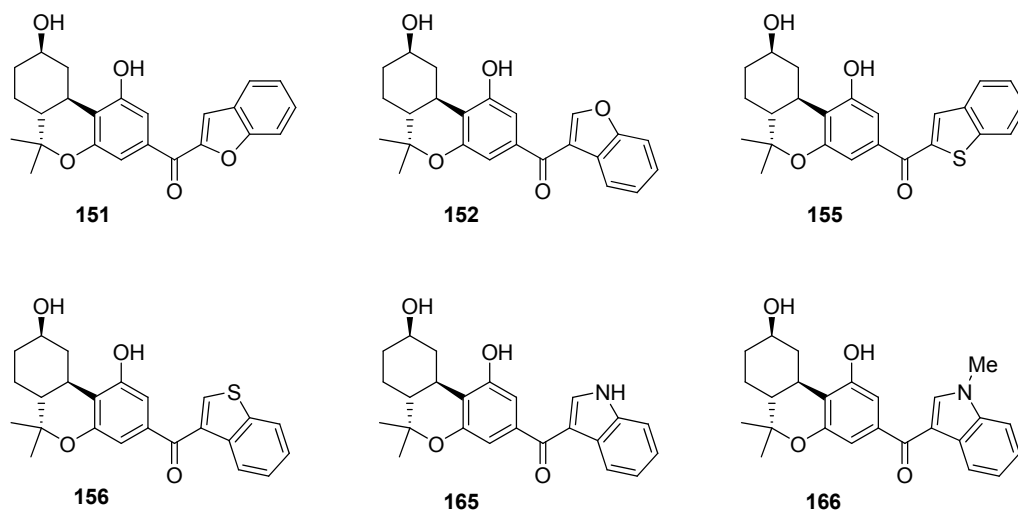
**Figure 8.1** Analogs belonging to group one.

In the second group, a six membered aromatic ring, substituted aromatic ring and a heteroaromatic ring was attached to C3 through a carbonyl linker (**148**, **159** - **164**).



**Figure 8.2** Analogs belonging to group two.

Finally, the third group consisted of a fused heteroaromatic rings attached to C3 through a carbonyl linker (**151**, **152**, **155**, **156**, **165** and **166**). The SAR of all the analogs was examined by measuring their respective affinities for the rat CB1 receptor (rCB1), mouse CB2 receptor (mCB2) and human CB2 receptor (hCB2) shown in **Table 8.1**.



**Figure 8.3** Analogs belonging to group three.



**Table 8.1** Affinities ( $K_i$ ) for CB1 and CB2 cannabinoid receptors.<sup>a</sup>

Compound	$K_i$ (nM) <sup>a</sup>		
	rCB1	mCB2	hCB2
<b>Group 1</b>			
<b>149</b>	>1000	>1000	>1000
<b>150</b>	>1000	>1000	N.A.
<b>153</b>	>1000	>1000	N.A.
<b>154</b>	1037	525	1551
<b>157</b>	>1000	>1000	>1000
<b>158</b>	>1000	>1000	N.A.
<b>Group 2</b>			
<b>148</b>	968	247	587
<b>159</b>	>1000	>1000	>1000
<b>160</b>	>1000	>1000	>1000
<b>161</b>	>1000	>1000	>1000
<b>162</b>	>1000	>1000	N.A.
<b>163</b>	460	370	N.A.
<b>164</b>	61.7	45.8	37.3

**Table 8.1** Continued.

<b>Group 3</b>			
<b>151</b>	1356	163.3	209.4
<b>152</b>	2880	169.2	118.2
<b>155</b>	156.6	152.1	113.1
<b>156</b>	1254	34.2	124.8
<b>165</b>	2400	60.4	158.6
<b>166</b>	3270	406	3006

<sup>a</sup> Affinities for CB1 and CB2 were determined using rat brain (CB1) or membranes from HEK293 cells expressing mouse or human CB2 and [<sup>3</sup>H]CP-55,940 as the radioligand following previously described procedures. K<sub>i</sub> values for these compounds were obtained from one experiment (8 point) run in triplicate when the two point data (run in triplicate) was less than 1000 nM.

All analogs belonging to group one (**149**, **150**, **153**, **154**, **157** and **158**) exhibited significantly diminished activity at both the CB1 and CB2 receptors (compared to **164**). This could be attributed to the to the lack of sufficient hydrophobic interaction of the five membered heteroaromatic ring with the hydrophobic pocket of the receptor which, in general, is the key factor for the affinity, potency and selectivity for the classical cannabinoids.<sup>111</sup> The reduced activity could also be due to the large desolvation penalties due to the polar nature of these rings. In the second group (**148**, **159** – **164**), benzoyl analog **148** showed reduced affinity and selectivity compared to Moore's tetrahydrocannabinol analog **120**. The reason for this observation is still unclear. One possibility is that the additional interaction of the C9 β-hydroxy group results in an unfavorable orientation of the C3 benzoyl group in the hydrophobic pocket of the

receptor. To further probe the interactions of the C3 aroyl group, a nitrogen atom was incorporated into the 2-, 3- and 4- positions of the aromatic ring (**159 - 162**). All of the pyridyl analogs exhibited a further decrease in activity at both the CB1 and CB2 receptors which could be a result from unfavorable electronic interactions within the receptor site. Incorporation of a fluorine atom at the *meta* position of the benzoyl group (**163**) improved binding at the CB1 receptor while slightly decreasing binding affinity at mCB2 (compared to **148**). Introduction of a lipophilic trifluoromethyl group (**164**) in the *meta* position of the benzoyl substituent yielded encouraging results. Binding affinities improved significantly for both receptors (rCB1 = 61.7 nM, mCB2 = 45.8 nM and hCB2 = 37.3 nM) compared to **148** and **163** and also showed a slight preference for CB2 over CB1 (1.7 fold). This is consistent with what the Moore group<sup>112</sup> observed with cannabinoid analogs containing a substituted phenyl ring at the 1' position. The *meta* substituted series resulted in higher affinities for both CB1 and CB2 when compared to their *para* substituted counterparts. Also, the presence of a *meta* electron withdrawing group enhanced CB1 binding affinities while the CB2 affinities were equivalent or slightly enhanced.

The third group (**151, 152, 155, 156, 165** and **166**) which incorporated fused bicyclic heteroaromatic groups connected to C3 through a carbonyl linker showed significant improvements in both affinity and selectivity for the CB2 receptor. The benzofuran series (**151** and **152**) displayed an eight fold and seventeen fold selectivity respectively for mCB2 over rCB1. The 2-benzofuran analog **151** displayed species selectivity for

mCB2 over hCB2 (1.3 fold) while the 3-benzofuran analog **152** slightly favored hCB2 over mCB2 (1.4 fold) but was 24.4 fold more selective for hCB2 over rCB1. Also, the binding affinity for rCB1 of **152** was two fold lower when compared to **151**. This observation can be attributed to the larger conformational space required by the 3-benzofuran analog (**152**) compared to the 2-benzofuran analog (**151**). Previous research in the Makriyannis group has shown that the space available in the receptor for interaction at the C3 site is larger for the CB2 receptor compared to that of the CB1 receptor.<sup>45</sup> Interestingly, the 2-benzothiophene analog **155** exhibited slight species selectivity for hCB2 which is the opposite of the 2-benzofuran analog **151**. The 3-benzothiophene analog **156** also showed the opposite species selectivity when compared to its 3-benzofuran counterpart **152** (3.6 fold for mCB2 over hCB2). Analog **156** was the most CB2 selective compound (36.7 fold more selective for mCB2 over rCB1) and exhibited an eight fold decrease in affinity for rCB1 when compared to **155**. To further probe the interaction of the heteroatom in the receptor, the O- or S-atom was replaced with a hydrogen bond donor/acceptor NH group. The presence of the indole nitrogen in **165** resulted in a slight reduction in affinity for mCB2 compared to that of **156** with a 17 fold selectivity for mCB2 over rCB1 and 2.6 fold species selectivity for mCB2 over hCB2. Capping of the indole nitrogen with a methyl group resulted in significantly diminished affinity at both rCB1 (>1000 nM) and mCB2 (406 nM). Arguably, this may be due to the inability of the nitrogen atom to interact with its counterpart amino acid residue due to the steric interactions of the introduced methyl group, signifying the importance of the heteroatom at that position.

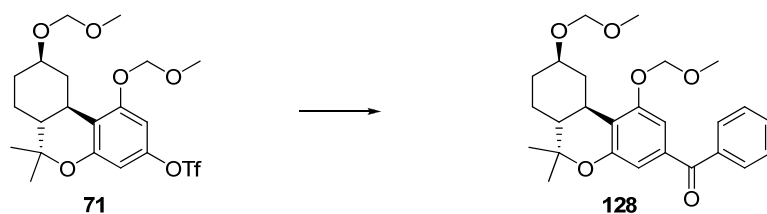
## 9 Conclusion

In conclusion, the synthesis of nineteen C3 heteroaryl cannabinoids has been described. The key steps in the synthesis were the carbonylative Stille reaction between an aryl triflate and heteroaryl stannanes, addition of heteroaryl groups to the aromatic aldehyde, and protecting group removal with TMSBr. All analogs showed at least micromolar affinity for the receptors and selectivity for CB2 over CB1. The 3-benzothiophene ( $K_i = 34.2$  nM), 3-trifluoromethylbenzene ( $K_i = 45.8$  nM) and 3-indole ( $K_i = 60.4$  nM) analogs proved to be the most potent compounds as well as the most selective towards CB2. This work also confirmed that the presence of a keto group at 1' imparts selectivity for the CB2 receptor, 5-membered heteroaromatic ring substituents at 1' are poor ligands, *meta* substituted phenyl rings at 1' are CB2 selective, 3-substituted fused bicyclic heteroaromatic rings favor CB2 over CB1 and the presence of a hydrogen bond acceptor heteroatom is important for strong binding. Functionalization of the phenyl or fused bicyclic heteroaromatic systems can also be envisioned to further probe the structural and electronic requirements of the CB2 receptor as well as introduction of an azide or isothiocyanate group to act as a covalent probe.

## 10 Experimental Section

### General:

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Varian Mercury Plus 300 ( $^1\text{H}$  300 MHz,  $^{13}\text{C}$  75 MHz) or a Varian Unity INOVA 500 ( $^1\text{H}$  500 MHz,  $^{13}\text{C}$  126 MHz) in either deuteriochloroform ( $\text{CDCl}_3$ ;  $^1\text{H}$  7.26 ppm,  $^{13}\text{C}$  77.0 ppm), deuterobenzene ( $\text{C}_6\text{D}_6$ ;  $^1\text{H}$  7.15 ppm,  $^{13}\text{C}$  128.0 ppm) or deuteromethanol ( $\text{CD}_3\text{OD}$ ;  $^1\text{H}$  3.31 and 4.90 ppm,  $^{13}\text{C}$  49.0 ppm). Chemical shifts are given in  $\delta$ , with multiplicities given as s (singlet), br (broad singlet), d (doublet), t (triplet), q (quartet), m (multiplet) or a combination thereof and  $J$  (coupling constants) given in hertz (Hz). IR spectra were recorded on a Nicolet 380 FT-IR using a NaCl plate. Mass spectral data was collected on either an Agilent 1100 Series LC-MS TOF ( $\text{ESI}^+$  or  $\text{APCI}^+$  source) or VG-70SE ( $\text{EI}^+$  source). Optical rotation data was collected on a JASCO DIP-370 digital polarimeter. Thin-layer chromatography (TLC) was performed using Sigma-Aldrich silica-gel, general-purpose TLC plates with UV indicator ( $\text{F}_{254}$ ). Flash chromatography was performed using Silicycle SiliaFlash F60 silica gel (230-400 mesh). All solvents used were purified using a solvent purification system. The purity of assayed compounds were of at least 95% and were verified using high performance liquid chromatography on an Agilent 1200 Series or a Beckman Coulter System Gold HPLC equipped with Daicel Chiralpak AD-H (4.6 x 250 mm), Luna C8(2) (1 x 250 mm) or Chiralcel OD-H (4.6 x 250 mm) column.



### General procedure for the carbonylative Stille coupling.

To a round bottom flask charged with a stir bar and triflate **71** (110 mg, 0.23 mmol) was added tributyl(phenyl)stannane (100 mg, 0.27 mmol), three 4 Å molecular sieve beads, three crystals of BHT, PdCl<sub>2</sub>(dppf)·CH<sub>2</sub>Cl<sub>2</sub> (*ca.* 7.5 mg, 0.01 mmol) and freshly flame dried LiCl (30 mg, 0.70 mmol). The flask was then sealed with a septum and placed under an atmosphere of CO followed by the addition of 1.2 mL of DMF. CO was bubbled through the mixture for 5 min and then the septum was quickly replaced with a three way tap equipped with a balloon of CO. The reaction mixture was warmed to 110 °C in an oil bath for 24 h. The black solution was then cooled to room temperature, adsorbed onto Celite and purified directly via flash column chromatography on silica gel eluting with 10%, 20% then 30% EtOAc/hexanes resulting in phenone **128** (66 mg, 66% yield) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.79 (d,  $J = 7.5$  Hz, 2H), 7.55 (t,  $J = 7.5$  Hz, 1H), 7.45 (t,  $J = 7.5$  Hz, 2H), 7.11 (d,  $J = 1.5$  Hz, 1H), 6.86 (d,  $J = 1.5$  Hz, 1H), 5.27 (d,  $J = 6.5$  Hz, 1H), 5.20 (d,  $J = 6.5$  Hz, 1H), 4.74 (dd,  $J = 13.3$  Hz, 6.8 Hz, 2H), 3.77 (m, 1H), 3.50 (s, 3H), 3.44 (m, 1H), 3.40 (s, 3H), 2.54 (td,  $J = 11.3$  Hz, 2.3 Hz, 1H), 2.22 (m, 1H), 1.92 (m, 1H), 1.58 (m, 1H), 1.46 (m, 1H), 1.39 (s, 3H), 1.20-1.11 (m, 2H), 1.04 (s, 3H)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  195.9, 156.4, 154.4, 137.6, 136.9, 132.1, 129.9, 128.1, 118.9, 114.4, 106.2, 94.8, 94.5, 77.3, 75.6, 56.5, 55.2, 48.5, 36.3, 34.3, 33.1, 27.6, 26.1, 18.8

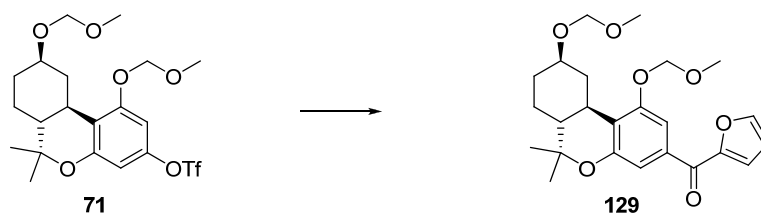
IR (thin film,  $\text{cm}^{-1}$ ): 2934, 1658, 1597, 1567, 1336, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{26}\text{H}_{32}\text{O}_6$ : 440.2199, found: 440.2200 (0.2 ppm error)

EI+ ( $m/z$ ): 440 ( $\text{M}^+$ , 35), 334 (100), 319 (24), 291 (39), 105 (29)

$[\alpha]_{\text{D}}^{23}$  -70 ( $c$  0.004, EtOAc)





Ketone **129** was prepared from triflate **71** (40 mg, 0.083 mmol) and tributyl(furan-2-yl)stannane (33 mg, 0.091 mmol) in 84% yield (30 mg) as a pale yellow oil.

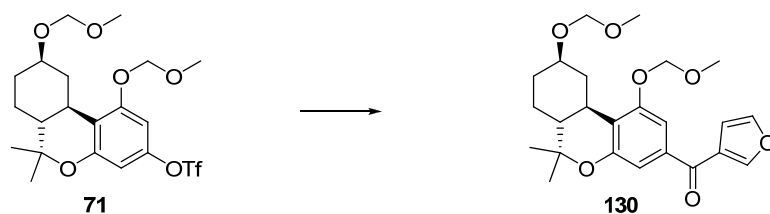
<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz): δ 7.69 (dd, *J* = 1.8 Hz, 0.6 Hz, 1H), 7.25 (dd, *J* = 3.6 Hz, 0.6 Hz, 1H), 7.19 (d, *J* = 1.5 Hz, 1H), 7.13 (d, *J* = 1.5 Hz, 1H), 6.57 (dd, *J* = 3.6 Hz, 1.8 Hz, 1H), 5.29 (d, *J* = 6.5 Hz, 1H), 5.21 (d, *J* = 6.5 Hz, 1H), 4.75 (dd, *J* = 9.3 Hz, 6.9 Hz, 2H), 3.77 (m, 1H), 3.51 (s, 3H), 3.46-3.40 (m, 4H), 2.54 (td, *J* = 11.3 Hz, 2.5 Hz, 1H), 2.23 (m, 1H), 1.94 (m, 1H), 1.62-1.42 (m, 5H), 1.23-1.06 (m, 5H)

<sup>13</sup>C NMR (CDCl<sub>3</sub>, 126 MHz): δ 181.7, 156.4, 154.7, 152.0, 147.0, 136.6, 120.6, 119.0, 113.1, 112.1, 105.8, 94.8, 94.5, 77.4, 75.6, 56.4, 55.2, 48.4, 36.2, 34.2, 33.1, 27.6, 26.1, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 2938, 1650, 1566, 1464, 1336, 1302, 1105, 1057

HR EI+ Mass Spec. Calculated for C<sub>24</sub>H<sub>30</sub>O<sub>7</sub>: 430.1992, found: 430.1982 (2.3 ppm error)

EI+(*m/z*): 430 (M<sup>+</sup>, 17), 364 (18), 324 (22), 258 (100), 243 (35), 215 (49), 149 (37)
$$[\alpha]_D^{23} -77 (c\ 0.014, \text{EtOAc})$$



Ketone **130** was prepared from triflate **71** (55 mg, 0.11 mmol) and tributyl(furan-3-yl)stannane (45 mg, 0.12 mmol) in 64% yield (31 mg) as a pale yellow oil.

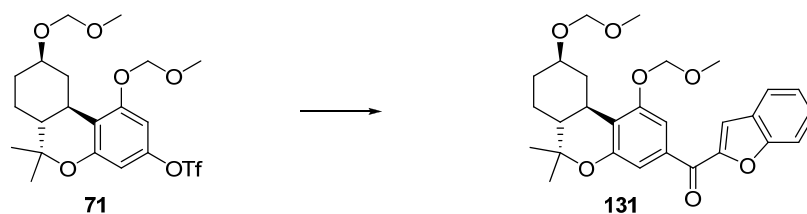
$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.96 (d,  $J = 0.5$  Hz, 1H), 7.47 (m, 1H), 7.11 (d,  $J = 1.5$  Hz, 1H), 6.99 (d,  $J = 1.5$  Hz, 1H), 6.89 (m, 1H), 5.26 (d,  $J = 6.5$  Hz, 1H), 5.20 (d,  $J = 6.5$  Hz, 1H), 4.74 (dd,  $J = 12.5$  Hz, 7.0 Hz, 2H), 3.76 (m 1H), 3.51 (s, 3H), 3.44-3.40 (m, 4H), 2.53 (td,  $J = 11.2$  Hz, 2.5 Hz, 1H), 2.22 (m, 1H), 1.95-1.90 (m, 1H), 1.57 (m, 1H), 1.51-1.40 (m, 4H), 1.20-1.05 (m, 5H)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  188.5, 156.5, 154.8, 148.5, 143.7, 138.1, 126.2, 118.8, 112.6, 110.2, 105.4, 94.8, 94.4, 77.4, 75.6, 56.4, 55.2, 48.4, 36.2, 34.2, 33.1, 27.6, 26.1, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 3131, 2935, 2876, 1651, 1567, 1508, 1402, 1336, 1158, 1105, 1078

HR ESI+ Mass Spec. Calculated for ( $\text{C}_{24}\text{H}_{30}\text{O}_7 + \text{Na}^+$ ): 453.1884, found: 453.1891 (1.5 ppm error)

$[\alpha]_{\text{D}}^{23}$  -89 ( $c$  0.011, EtOAc)



Ketone **131** was prepared from triflate **71** (41 mg, 0.085 mmol) and (benzofuran-2-yl)tributylstannane (38 mg, 0.094 mmol) in 76% yield (31 mg) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.71 (d,  $J = 8.3$  Hz, 1H), 7.64 (d,  $J = 8.3$  Hz, 1H), 7.55 (s, 1H), 7.48 (t,  $J = 7.8$  Hz, 1H), 7.32 (t,  $J = 7.8$  Hz, 1H), 7.25 (d,  $J = 1.5$  Hz, 1H), 7.19 (d,  $J = 1.5$  Hz, 1H), 5.31 (d,  $J = 6.5$  Hz, 1H), 5.23 (d,  $J = 6.5$  Hz, 1H), 4.75 (dd,  $J = 12.5$  Hz, 7.0 Hz, 2H), 3.78 (m, 1H), 3.53 (s, 3H), 3.47-3.41 (m, 4H), 2.56 (td,  $J = 11.3$  Hz, 2.5 Hz, 1H), 2.24 (m, 1H), 1.95 (m, 1H), 1.60 (m, 1H), 1.52-1.41 (m, 4H), 1.21-1.12 (m, 2H), 1.08 (s, 3H)

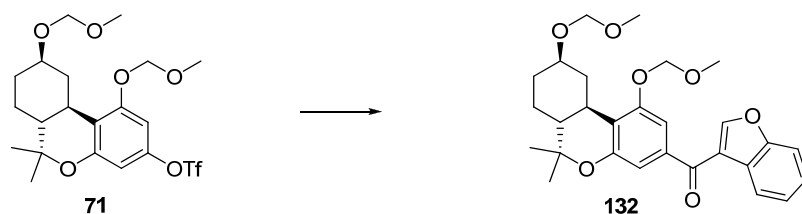
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  183.6, 156.5, 156.0, 154.7, 152.0, 136.6, 128.2, 127.0, 123.8, 123.3, 119.4, 116.6, 113.2, 112.6, 105.9, 94.8, 94.5, 77.5, 75.6, 56.5, 55.2, 48.4, 36.2, 34.3, 33.1, 27.6, 26.1, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 2931, 1653, 1559, 1541, 1338, 1154, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{32}\text{O}_7$ : 480.2148, found: 480.2161 (2.7 ppm error)

EI+ ( $m/z$ ): 480 ( $\text{M}^+$ , 23), 420 (18), 374 (47), 314 (48), 288 (27), 269 (41), 258 (100), 215 (56), 145 (27)

$[\alpha]_{\text{D}}^{23}$  -64 ( $c$  0.012, EtOAc)



Ketone **132** was prepared from triflate **71** (46 mg, 0.095 mmol) and (benzofuran-2-yl)tributylstannane (43 mg, 0.11 mmol) in 68% yield (31 mg) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.26-8.24 (m, 1H), 8.16 (s, 1H), 7.55 (m, 1H), 7.41-7.37 (m, 2H), 7.16 (d,  $J = 1.5$  Hz, 1H), 7.03 (d,  $J = 1.5$  Hz, 1H), 5.29 (d,  $J = 6.5$  Hz, 1H), 5.21 (d,  $J = 6.5$  Hz, 1H), 4.75 (dd,  $J = 12.8$  Hz, 6.8 Hz, 2H), 3.81-3.74 (m, 1H), 3.51 (s, 3H), 3.47-3.40 (m, 4H), 2.55 (td,  $J = 11.3$  Hz, 2.5 Hz, 1H), 2.23 (m, 1H), 1.94 (m, 1H), 1.59 (td,  $J = 12.3$  Hz, 2.5 Hz, 1H), 1.52-1.42 (m, 4H), 1.21-1.11 (m, 2H), 1.07 (s, 3H)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  189.3, 156.6, 155.5, 154.8, 152.2, 138.5, 125.7, 125.3, 124.4, 122.9, 120.8, 118.8, 112.5, 111.4, 105.5, 94.8, 94.4, 77.4, 75.6, 56.4, 55.2, 48.4, 36.2, 34.2, 33.1, 27.6, 26.1, 18.8

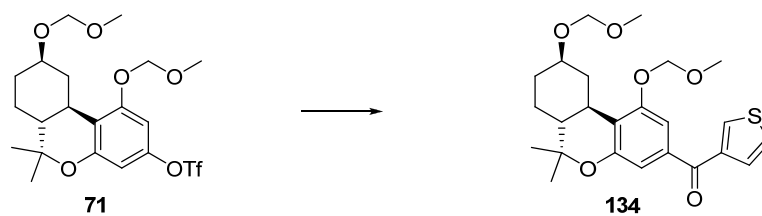
IR (thin film,  $\text{cm}^{-1}$ ): 2983, 2935, 2880, 2815, 1647, 1567, 1547, 1450, 1423, 1401, 1367, 1155, 1056

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{32}\text{O}_7$ : 480.2148, found: 480.2135 (2.7 ppm error)

EI+ ( $m/z$ ): 480 ( $\text{M}^+$ , 26), 374 (91), 331 (50), 145 (100)

$[\alpha]_D^{23}$  -76 ( $c$  0.010, EtOAc)





Ketone **134** was prepared from triflate **71** (73 mg, 0.15 mmol) and tributyl(thiophen-3-yl)stannane (62 mg, 0.17 mmol) in 81% yield (54 mg) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.96 (dd,  $J = 2.8$  Hz, 1.3 Hz, 1H), 7.58 (dd,  $J = 5.3$  Hz, 1.3 Hz, 1H), 7.10 (d,  $J = 1.5$  Hz, 1H), 6.96 (d,  $J = 1.5$  Hz, 1H), 5.27 (d,  $J = 6.5$  Hz, 1H), 5.19 (d,  $J = 6.5$  Hz, 1H), 4.73 (dd,  $J = 12.8$  Hz, 6.8 Hz, 2H), 3.79-3.73 (m, 1H), 3.50 (s, 3H), 3.43 (m, 1H), 3.39 (s, 3H), 2.53 (td,  $J = 11.2$  Hz, 2.3 Hz, 1H), 2.21 (m, 1H), 1.92 (m, 1H), 1.57 (m, 1H), 1.51-1.39 (m, 5H), 1.14 (m, 1H), 1.04 (s, 3H)

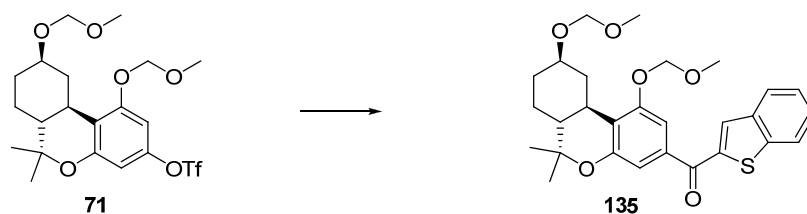
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  189.1, 156.3, 154.5, 141.0, 137.8, 133.8, 128.6, 125.9, 118.6, 113.3, 105.8, 94.8, 94.4, 77.3, 75.6, 56.4, 55.1, 48.4, 36.2, 34.2, 33.0, 27.6, 26.0, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 3106, 2935, 2879, 2824, 1651, 1567, 1510, 1401, 1334, 1105, 923, 751

HR EI+ Mass Spec. Calculated for  $\text{C}_{24}\text{H}_{30}\text{O}_6\text{S}$ : 446.1763, found: 446.1776 (2.9 ppm error)

EI+ ( $m/z$ ): 446 ( $\text{M}^+$ , 3), 273 (18), 269 (100), 265 (38), 207 (26)

$[\alpha]_{\text{D}}^{23}$  -73 ( $c$  0.020, EtOAc)



Ketone **135** was prepared from triflate **71** (65 mg, 0.13 mmol) and (benzo[*b*]thiophen-2-yl)tributylstannane (62 mg, 0.15 mmol) in 64% yield (40.5 mg) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.94 (s, 1H), 7.89 (app t,  $J$  = 8.5 Hz, 2H), 7.48 (t,  $J$  = 7.8 Hz, 1H), 7.40 (t,  $J$  = 7.8 Hz, 1H), 7.16 (d,  $J$  = 1.5 Hz, 1H), 7.07 (d,  $J$  = 1.5 Hz, 1H), 5.29 (d,  $J$  = 6.5 Hz, 1H), 5.21 (d,  $J$  = 6.5 Hz, 1H), 4.75 (dd,  $J$  = 12.8 Hz, 6.5 Hz, 2H), 3.78 (m, 1H), 3.51 (s, 3H), 3.48-3.41 (m, 4H), 2.56 (td,  $J$  = 11.3 Hz, 2.2 Hz, 1H), 2.24 (m, 1H), 1.95 (m, 1H), 1.61 (m, 1H), 1.53-1.43 (m, 4H), 1.17 (m, 1H), 1.08 (s, 3H)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  188.7, 156.5, 154.7, 142.9, 142.6, 139.1, 137.1, 132.1, 127.3, 126.1, 124.9, 122.8, 118.9, 113.1, 105.9, 94.8, 94.5, 77.5, 75.6, 56.5, 55.2, 48.5, 36.3, 34.3, 33.1, 27.6, 26.1, 18.8

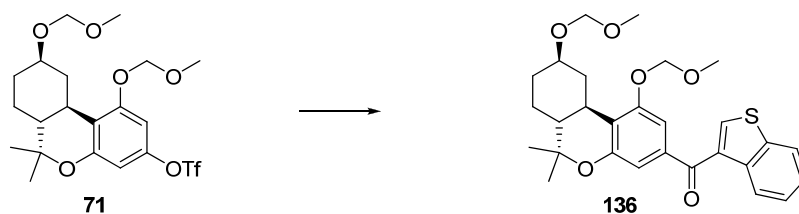
IR (thin film,  $\text{cm}^{-1}$ ): 2933, 1636, 1567, 1508, 1338, 1156, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{32}\text{O}_6\text{S}$ : 496.1920, found: 496.1909 (2.2 ppm error)

EI+ ( $m/z$ ): 496 ( $\text{M}^+$ , 55), 390 (100), 347 (30), 267 (36), 161 (47)

$[\alpha]_D^{23}$  -63 ( $c$  0.012, EtOAc)





Ketone **136** was prepared from triflate **71** (83 mg, 0.17 mmol) and (benzo[*b*]thiophen-3-yl)tributylstannane (80 mg, 0.19 mmol) in 69% yield (58 mg) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.55 (dd,  $J = 7.5$  Hz, 0.5 Hz, 1H), 8.08 (s, 1H), 7.88 (d,  $J = 7.5$  Hz, 1H), 7.49 (dt,  $J = 8.3$  Hz, 1.3 Hz, 1H), 7.42 (dt,  $J = 8.3$  Hz, 1.3 Hz, 1H), 7.16 (d,  $J = 1.5$  Hz, 1H), 6.98 (d,  $J = 1.5$  Hz, 1H), 5.28 (d,  $J = 6.5$  Hz, 1H), 5.21 (d,  $J = 6.5$  Hz, 1H), 4.75 (dd,  $J = 12.8$  Hz, 6.8 Hz, 2H), 3.81-3.74 (m, 1H), 3.51 (s, 3H), 3.46 (m, 1H), 3.40 (s, 3H), 2.55 (td,  $J = 11.3$  Hz, 2.3 Hz, 1H), 2.23 (m, 1H), 1.93 (m, 1H), 1.59 (m, 1H), 1.50-1.40 (m, 4H), 1.20-1.11 (m, 2H), 1.06 (s, 3H)

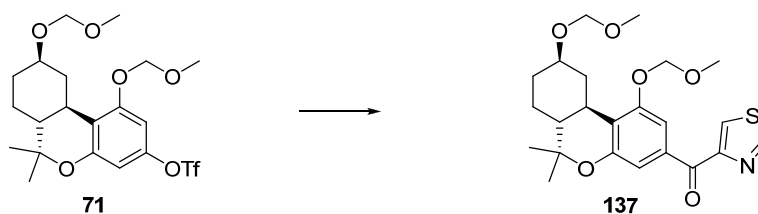
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  189.9, 156.4, 154.5, 139.9, 138.5, 138.1, 137.4, 134.4, 125.5, 125.4, 125.1, 122.2, 118.7, 113.5, 106.0, 94.8, 94.4, 77.3, 75.6, 56.4, 55.1, 48.4, 36.2, 34.2, 33.0, 27.6, 26.0, 18.7

IR (thin film,  $\text{cm}^{-1}$ ): 3099, 2934, 2878, 1645, 1567, 1056, 1043

HR EI+ Mass Spec. Calculated for  $\text{C}_{28}\text{H}_{32}\text{O}_6\text{S}$ : 496.1920, found: 496.1904 (3.2 ppm error)

EI+ ( $m/z$ ): 496 ( $\text{M}^+$ , 35), 390 (70), 314 (100), 272 (42), 257 (42), 207 (41), 161 (48)

$[\alpha]_{\text{D}}^{23} -73$  ( $c$  0.012, EtOAc)



Ketone **137** was prepared from triflate **71** (52 mg, 0.11 mmol) and 4-(tributylstannyl)thiazole (44 mg, 0.12 mmol) in 76% yield (36.5 mg) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.88 (d,  $J = 2.0$  Hz, 1H), 8.24 (d,  $J = 2.0$  Hz, 1H), 7.36 (d,  $J = 1.5$  Hz, 1H), 7.31 (d,  $J = 1.5$  Hz, 1H), 5.28 (d,  $J = 6.5$  Hz, 1H), 5.21 (d,  $J = 6.5$  Hz, 1H), 4.73 (dd,  $J = 6.8$  Hz, 1.8 Hz, 2H), 3.76 (m, 1H), 3.50 (s, 3H), 3.42 (m, 1H), 3.38 (s, 3H), 2.53 (td,  $J = 11.2$  Hz, 1.5 Hz, 1H), 2.22 (m, 1H), 1.91 (m, 1H), 1.56 (m, 1H), 1.49-1.39 (m, 4H), 1.19-1.11 (m, 2H), 1.04 (s, 3H)

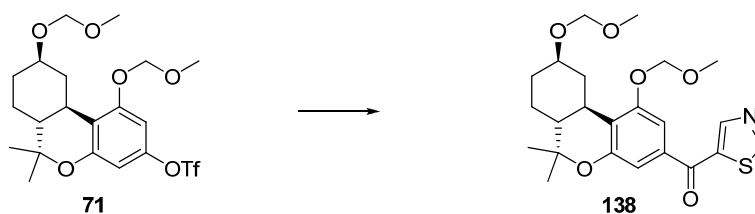
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  186.4, 156.3, 155.2, 154.5, 152.7, 136.5, 127.5, 119.5, 114.4, 106.5, 94.8, 94.5, 77.2, 75.6, 56.4, 55.1, 48.4, 36.2, 34.3, 33.0, 27.6, 26.0, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 3101, 2934, 2877, 2824, 1653, 1567, 1400, 1369, 1154, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{23}\text{H}_{29}\text{NO}_6\text{S}$ : 447.1716, found: 447.1719 (0.7 ppm error)

EI+ ( $m/z$ ): 447 ( $\text{M}^+$ , 34), 354 (22), 341 (100), 326 (30), 298 (47), 273 (46), 271 (66), 212 (37), 208 (20), 177 (53), 153 (24), 149 (41), 112 (57), 69 (32)

$[\alpha]_D^{23}$  -74 ( $c$  0.010, EtOAc)



Ketone **138** was prepared from triflate **71** (67 mg, 0.14 mmol) and 5-(tributylstannyl)thiazole (57 mg, 0.15 mmol) in 44% yield (27 mg) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  9.03 (s, 1H), 8.41 (s, 1H), 7.13 (d,  $J = 1.5$  Hz, 1H), 7.02 (d,  $J = 1.5$  Hz, 1H), 5.27 (d,  $J = 6.5$  Hz, 1H), 5.21 (d,  $J = 6.5$  Hz, 1H), 4.74 (dd,  $J = 12.0$  Hz, 7.0 Hz, 2H), 3.76 (m, 1H), 3.50 (s, 3H), 3.44-3.39 (m, 4H), 2.54 (td,  $J = 10.8$  Hz, 2.5 Hz, 1H), 2.22 (m, 1H), 1.92 (m, 1H), 1.58 (td,  $J = 11.7$  Hz, 2.3 Hz, 1H), 1.51-1.39 (m, 4H), 1.20-1.05 (m, 5H)

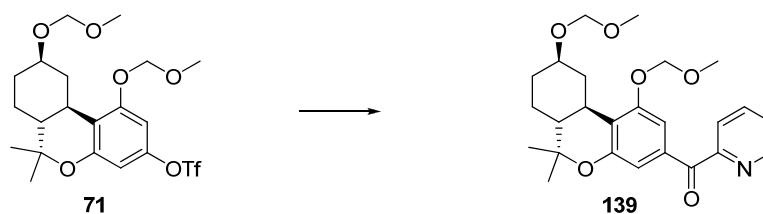
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  186.4, 158.9, 156.6, 154.9, 148.9, 139.1, 136.7, 119.5, 113.0, 105.6, 94.8, 94.4, 77.5, 75.6, 56.4, 55.2, 48.3, 36.1, 34.2, 33.0, 27.6, 26.0, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 2936, 2880, 2825, 1647, 1569, 1338, 1154, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{23}\text{H}_{29}\text{NO}_6\text{S}$ : 447.1716, found: 447.1708 (1.8 ppm error)

EI+ ( $m/z$ ): 447 ( $\text{M}^+$ , 1), 149 (13), 97 (14), 95 (19), 83 (24), 81 (43), 69 (100)

$[\alpha]_D^{23}$  -78 ( $c$  0.007, EtOAc)



Ketone **139** was prepared from triflate **71** (60 mg, 0.12 mmol) and 2-(tributylstannyl)pyridine (50 mg, 0.14 mmol) in 58% yield (32 mg) as a pale yellow oil which turns green upon standing.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.89 (d,  $J = 2.0$  Hz, 1H), 8.24 (d,  $J = 2.0$  Hz, 1H), 7.36 (d,  $J = 1.5$  Hz, 1H), 7.31 (d,  $J = 1.5$  Hz, 1H), 5.28 (d,  $J = 6.5$  Hz, 1H), 5.21 (d,  $J = 6.5$  Hz, 1H), 4.73 (dd,  $J = 12.3$  Hz, 6.8 Hz, 2H), 3.76 (m, 1H), 3.50 (s, 3H), 3.44-3.38 (m, 4H), 2.53 (td,  $J = 11.2$  Hz, 2.5 Hz, 1H), 2.21 (m, 1H), 1.91 (m, 1H), 1.56 (m, 1H), 1.49-1.39 (m, 4H), 1.19-1.07 (m, 2H), 1.04 (s, 3H)

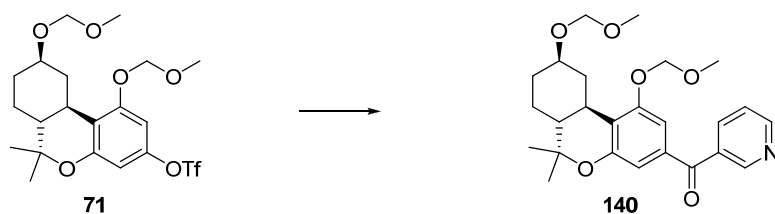
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  186.4, 156.3, 155.2, 154.5, 152.7, 136.5, 127.5, 119.5, 114.4, 106.5, 94.8, 94.5, 77.2, 75.6, 56.4, 55.1, 48.4, 36.2, 34.3, 33.0, 27.6, 26.0, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 3101, 2934, 2877, 2824, 1653, 1567, 1337, 1154, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{25}\text{H}_{31}\text{NO}_6$ : 441.2151, found: 441.2158 (1.6 ppm error)

EI+ ( $m/z$ ): 441 ( $\text{M}^+$ , 3), 274 (33), 272 (60), 269 (100), 267 (68), 253 (36), 231 (74)

$[\alpha]_{\text{D}}^{23}$  -36 ( $c$  0.007, EtOAc)



Ketone **140** was prepared from triflate **71** (65 mg, 0.13 mmol) and 3-(tributylstannyl)pyridine (54 mg, 0.15 mmol) in 83% yield (49 mg) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.99 (bs, 1H), 8.78 (bs, 1H), 8.09 (d,  $J = 7.5$  Hz, 1H), 7.42 (dd,  $J = 7.5$  Hz, 5.0 Hz, 1H), 7.13 (d,  $J = 1.5$  Hz, 1H), 6.85 (d,  $J = 1.5$  Hz, 1H), 5.27 (d,  $J = 6.8$  Hz, 1H), 5.21 (d,  $J = 6.8$  Hz, 1H), 4.74 (dd,  $J = 12.3$  Hz, 6.8 Hz, 2H), 3.77 (m, 1H), 3.50 (s, 3H), 3.43 (m, 1H), 3.40 (s, 3H), 2.54 (td,  $J = 11.3$  Hz, 2.3 Hz, 1H), 2.22 (m, 1H), 1.93 (m, 1H), 1.58 (m, 1H), 1.51-1.31 (m, 4H), 1.20-1.10 (m, 2H), 1.05 (s, 3H)

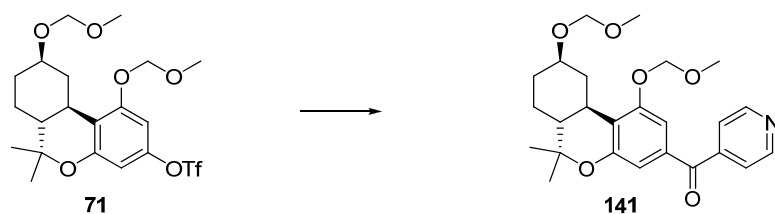
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  194.1, 156.6, 154.7, 152.6, 150.8, 137.1, 136.0, 123.2, 119.7, 114.4, 106.0, 94.8, 94.4, 77.5, 75.6, 56.5, 55.2, 48.4, 36.2, 34.3, 33.1, 27.6, 26.0, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 2933, 1653, 1559, 1339, 1154

HR EI+ Mass Spec. Calculated for  $\text{C}_{25}\text{H}_{31}\text{NO}_6$ : 441.2151, found: 441.2137 (3.2 ppm error)

EI+ ( $m/z$ ): 441 ( $\text{M}^+$ , 21), 380 (20), 335 (100), 320 (22), 292 (40), 106 (25)

$[\alpha]_{\text{D}}^{23}$  -75 ( $c$  0.010, EtOAc)



Ketone **141** was prepared from triflate **71** (54 mg, 0.11 mmol) and 4-(tributylstannyl)pyridine (45 mg, 0.12 mmol) in 84% yield (41 mg) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.77 (d,  $J = 4.5$  Hz, 2H), 7.56 (d,  $J = 6.0$  Hz, 2H), 7.15 (d,  $J = 1.5$  Hz, 1H), 6.81 (d,  $J = 1.5$  Hz, 1H), 5.27 (d,  $J = 6.5$  Hz, 1H), 5.21 (d,  $J = 6.5$  Hz, 1H), 4.74 (dd,  $J = 11.8$  Hz, 6.8 Hz, 2H), 3.76 (m, 1H), 3.50 (s, 3H), 3.44-3.39 (m, 4H), 2.54 (dt,  $J = 11.3$  Hz, 2.3 Hz, 1H), 2.22 (m, 1H), 1.93 (m, 1H), 1.57 (m, 1H), 1.51-1.39 (m, 4H), 1.19-1.06 (m, 2H), 1.04 (s, 3H)

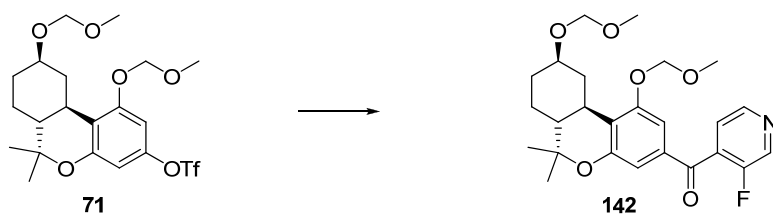
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  194.4, 156.7, 154.7, 150.2, 144.5, 135.2, 122.8, 120.1, 114.6, 105.9, 94.8, 94.4, 77.6, 75.6, 56.5, 55.2, 48.4, 36.2, 34.3, 33.1, 27.6, 26.0, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 2936, 2879, 2824, 1669, 1569, 1424, 1405, 1338, 1155, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{25}\text{H}_{31}\text{NO}_6$ : 441.2151, found: 441.2137 (3.2 ppm error)

EI+ ( $m/z$ ): 441 ( $\text{M}^+$ , 19), 365 (11), 335 (100), 320 (23), 292 (50), 106 (37)

$[\alpha]_{\text{D}}^{23}$  -79 ( $c$  0.012, EtOAc)



Ketone **142** was prepared from triflate **71** (77 mg, 0.16 mmol) and 4-(tributylstannyl)-3-fluoropyridine (68 mg, 0.18 mmol) in 51% yield (36 mg) as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.59 (s, 1H), 8.54 (d,  $J = 4.5$  Hz, 1H), 7.35 (t,  $J = 5.3$  Hz, 1H), 7.23 (d,  $J = 1.5$  Hz, 1H), 6.74 (s, 1H), 5.27 (d,  $J = 6.8$  Hz, 1H), 5.21 (d,  $J = 6.8$  Hz, 1H), 4.73 (dd,  $J = 11.5$  Hz, 7.0 Hz, 2H), 3.76 (m, 1H), 3.50 (s, 3H), 3.42-3.39 (m, 4H), 2.52 (td,  $J = 11.3$  Hz, 2.3 Hz, 1H), 2.22 (m, 1H), 1.92 (m, 1H), 1.54 (td,  $J = 11.6$  Hz, 2.2 Hz, 1H), 1.45 (m, 1H), 1.38 (s, 3H), 1.18-1.07 (m, 2H), 1.03 (s, 3H)

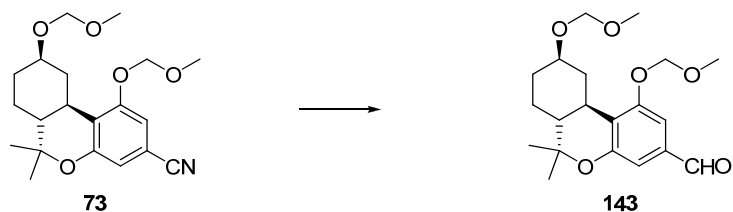
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  190.5, 155.9 (d,  $J_{\text{CF}} = 251.0$  Hz), 145.8 (d,  $J_{\text{CF}} = 5.4$  Hz), 139.3 (d,  $J_{\text{CF}} = 26.5$  Hz), 135.1, 134.0, 133.9, 123.0, 121.2, 114.8, 104.9, 94.8, 94.5, 77.6, 75.5, 56.5, 55.2, 48.3, 36.1, 34.3, 33.0, 27.5, 26.0, 18.7

IR (thin film,  $\text{cm}^{-1}$ ): 2931, 2879, 1671, 1570, 1412, 1338, 1154, 1105, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{25}\text{H}_{30}\text{FNO}_6$ : 459.2057, found: 459.2051 (1.3 ppm error)

EI+ ( $m/z$ ): 459 ( $\text{M}^+$ , 18), 353 (100), 338 (17), 310 (45), 124 (25)

$[\alpha]_{\text{D}}^{23}$  -60 ( $c$  0.012, EtOAc)



Nitrile **73** (530 mg, 1.47 mmol) was dissolved in 10 mL of  $\text{CH}_2\text{Cl}_2$ , cooled to  $-78^\circ\text{C}$  and stirred for 10 min. DIBAL (520  $\mu\text{L}$ , 2.93 mmol) was then added drop wise and stirred for 45 min. Excess DIBAL was quenched with acetone at  $-78^\circ\text{C}$  and then the reaction mixture was stirred with saturated Rochelle's salt at room temperature until the emulsion subsided. EtOAc was added; organic layer was washed with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude product was then purified on silica gel eluting with 30% then 40% EtOAc/hexanes resulting in aldehyde **143** (516 mg, 96%) as a clear, colorless oil.



$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  9.81 (s, 1H), 7.10 (s, 1H), 6.97 (s, 1H), 5.26 (d,  $J = 6.5$  Hz, 1H), 5.20 (d,  $J = 6.5$  Hz, 1H), 4.72 (m, 2H), 3.74 (m, 1H), 3.49 (s, 3H), 3.42-3.37 (m, 4H), 2.51 (td,  $J = 11.3$  Hz, 2.1 Hz, 1H), 2.20 (m, 1H), 1.91 (m, 1H), 1.59-1.38 (m, 5H), 1.26-1.03 (m, 5H)

$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  191.7, 156.9, 155.3, 136.1, 120.9, 114.3, 104.6, 94.8, 94.4, 77.4, 75.6, 56.4, 55.1, 48.3, 36.1, 34.4, 33.0, 27.5, 26.0, 18.7

IR (thin film,  $\text{cm}^{-1}$ ): 2938, 2879, 2726, 1698, 1576, 1433, 1385, 1154, 1056

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{28}\text{O}_6$ : 364.1886, found: 364.1890 (1.1 ppm error)

EI+ ( $m/z$ ): 364 ( $\text{M}^+$ , 19), 288 (13), 258 (100), 243 (31), 215 (70), 69 (25)

$[\alpha]_{\text{D}}^{23}$  -88 ( $c$  0.011, EtOAc)



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$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  7.56 (d,  $J = 7.5$  Hz, 1H), 7.49-7.47 (m, 1H), 7.44-7.40 (m, 1H), 7.26-7.22 (m, 1H), 7.10 (d,  $J = 1.5$  Hz, 1H), 6.83 (d,  $J = 1.5$  Hz, 1H), 5.26 (d,  $J = 6.8$  Hz, 1H), 5.19 (d,  $J = 6.8$  Hz, 1H), 4.74 (dd,  $J = 12.8$  Hz, 6.8 Hz, 2H), 3.76 (m, 1H), 3.50 (s, 3H), 3.43 (m, 1H), 3.39 (s, 3H), 2.53 (td,  $J = 11.2$  Hz, 2.5 Hz, 1H), 2.21 (m, 1H), 1.92 (m, 1H), 1.57 (m, 1H), 1.45 (m, 1H), 1.39 (s, 3H), 1.19-1.07 (m, 2H), 1.04 s, 3H)

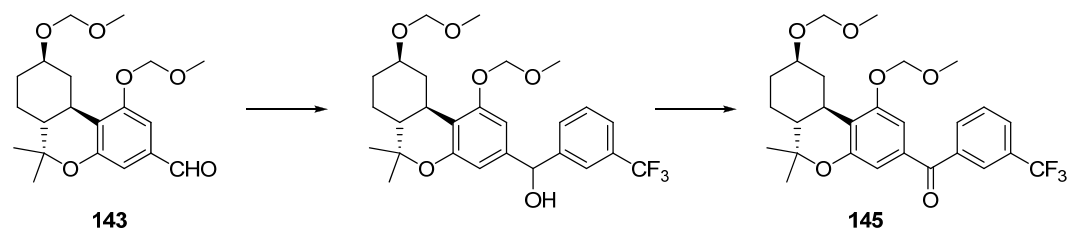
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  194.4, 162.3 (d,  $J_{\text{CF}} = 247.7$  Hz), 156.4, 154.4, 139.6 (d,  $J_{\text{CF}} = 6.2$  Hz), 136.2, 129.8 (d,  $J_{\text{CF}} = 7.8$  Hz), 125.6, 119.2, 119.0, 116.6 (d,  $J_{\text{CF}} = 22.4$  Hz), 114.2, 106.1, 94.8, 94.4, 77.4, 75.5, 56.4, 55.1, 48.4, 36.2, 34.2, 33.0, 27.5, 26.0, 18.7

IR (thin film,  $\text{cm}^{-1}$ ): 2935, 2879, 1653, 1568, 1558, 1338, 1155, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{26}\text{H}_{31}\text{FO}_6$ : 458.2105, found: 458.2120 (3.3 ppm error)

EI+ ( $m/z$ ): 458 ( $\text{M}^+$ , 34), 352 (100), 309 (48), 219 (26), 149 (52), 123 (94), 71 (32), 69 (33)

$[\alpha]_{\text{D}}^{23}$  -68 ( $c$  0.020, EtOAc)



Ketone **145** was prepared from aldehyde **143** (62 mg, 0.17 mmol) and 1-bromo-3-(trifluoromethyl)benzene (180 mg, 0.80 mmol) in 81% yield (65 mg) over the 2 steps as a pale yellow oil.

$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.05 (s, 1H), 7.97 (d,  $J = 7.5$  Hz, 1H), 7.81 (d,  $J = 7.5$  Hz, 1H), 7.59 (t,  $J = 7.5$  Hz, 1H), 7.09 (d,  $J = 1.5$  Hz, 1H), 6.84 (d,  $J = 1.5$  Hz, 1H), 5.26 (d,  $J = 6.8$  Hz, 1H), 5.19 (d,  $J = 6.8$  Hz, 1H), 4.74 (dd,  $J = 12.5$  Hz, 7.0 Hz, 2H), 3.77 (m, 1H), 3.50 (s, 3H), 3.43 (m, 1H), 3.39 (s, 3H), 2.54 (td,  $J = 11.3$  Hz, 2.3 Hz, 1H), 2.25 (m, 1H), 1.93 (m, 1H), 1.58 (m, 1H), 1.47 (m, 1H), 1.39 (s, 3H), 1.19-1.11 (m, 2H), 1.05 (s, 3H)

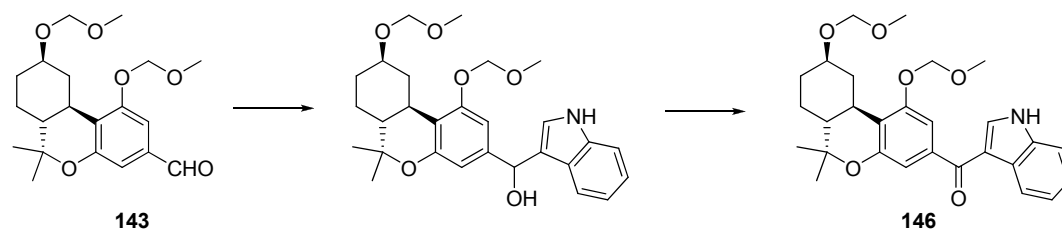
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  194.4, 156.5, 154.7, 138.3, 136.0, 133.0, 130.7 (q,  $J_{\text{CF}} = 32.7$  Hz), 128.8, 128.5 (q,  $J_{\text{CF}} = 3.1$  Hz), 126.6 (q,  $J_{\text{CF}} = 3.5$  Hz), 124.0 (q,  $J_{\text{CF}} = 272.5$  Hz), 119.5, 114.1, 106.3, 94.8, 94.3, 77.5, 75.6, 56.4, 55.2, 48.3, 36.2, 34.2, 33.1, 27.5, 26.0, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 2979, 2942, 2882, 1653, 1569, 1340, 1296, 1129, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{27}\text{H}_{31}\text{F}_3\text{O}_6$ : 508.2073, found: 508.2079 (1.2 ppm error)

EI+ ( $m/z$ ): 508 ( $\text{M}^+$ , 4), 402 (22), 319 (100), 215 (36), 173 (95), 145 (29)

$[\alpha]_{\text{D}}^{23}$  -57 ( $c$  0.017, EtOAc)



To aldehyde **143** (99 mg, 0.27 mmol) and indole (35 mg, 0.30 mmol) in 500  $\mu$ L of MeOH at 0  $^{\circ}$ C was added 30  $\mu$ L of 50% KOH dropwise. The reaction flask was then sealed with a Teflon cap and stirred overnight gradually warming to room temperature. Saturated  $\text{NH}_4\text{Cl}$  was then added, extracted with EtOAc, washed with brine and dried over  $\text{MgSO}_4$ . The crude addition product was purified via flash column chromatography on silica gel eluting with 30%, 50% then 80% EtOAc/hexanes. The alcohol was then treated with  $\text{MnO}_2$  (283 mg, 3.26 mmol) in 10 mL of  $\text{CH}_2\text{Cl}_2$  at rt for 12 h. The solids were removed by filtering through Celite and then the solvent was removed under reduced pressure. The crude ketone was then purified via flash column chromatography on silica gel eluting with 30% then 50% EtOAc/hexanes resulting in pure ketone **146** (67 mg, 52% over 2 steps) as a clear yellow oil.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.28 (dd,  $J$  = 6.5 Hz, 2.0 Hz, 1H), 7.85 (s, 1H), 7.48 (dd,  $J$  = 6.8 Hz, 1.8 Hz, 1H), 7.28-7.23 (m, 2H), 7.07 (d,  $J$  = 1.5 Hz, 1H), 6.86 (d,  $J$  = 1.5 Hz, 1H), 5.29 (d,  $J$  = 6.8 Hz, 1H), 5.22 (d,  $J$  = 6.8 Hz, 1H), 4.72 (s, 2H), 3.74 (m, 1H), 3.50-3.48 (m, 4H), 3.37 (s, 3H), 2.56 (td,  $J$  = 11.3 Hz, 2.3 Hz, 1H), 2.19 (m, 1H), 1.92 (m, 1H), 1.53 (m, 1H), 1.46-1.36 (m, 4H), 1.18 (m, 1H), 1.09-1.02 (m, 4H)

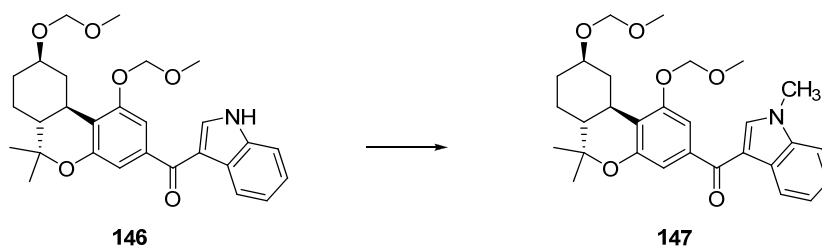
$^{13}\text{C}$  NMR (CDCl<sub>3</sub>, 126 MHz):  $\delta$  193.0, 157.7, 155.9, 141.3, 138.5, 137.2, 127.8, 124.6, 123.4, 123.0, 119.0, 116.9, 113.1, 113.0, 107.2, 96.0, 95.7, 78.4, 77.4, 56.7, 55.5, 50.0, 37.9, 35.4, 34.3, 28.0, 27.0, 19.1

IR (thin film, cm<sup>-1</sup>): 3246(br), 2978, 2934, 2875, 2816, 1737, 1604, 1563, 1519, 1433, 1371, 1244, 1153, 1056, 1045

HR EI+ Mass Spec. Calculated for C<sub>28</sub>H<sub>33</sub>NO<sub>6</sub>: 479.2308, found: 479.2291 (3.5 ppm error)

EI+ ( $m/z$ ): 479 (35, M+), 373 (84), 330 (21), 144 (100), 130 (46)

$[\alpha]_D^{23}$  -83 ( $c$  0.016, EtOAc)



To ketone **146** (24 mg, 0.05 mmol) in 500  $\mu$ L DMF under  $N_2$  at room temperature was added a spatula tip of NaH and stirred for 10 minutes. MeI (56 mg, 25  $\mu$ L) was then added and stirred overnight. The reaction mixture was then directly absorbed onto Celite and purified via flash column chromatography on silica gel eluting with 60% EtOAc/hexanes resulting in **147** (24 mg, 97%) as a clear, colorless oil.



$^1\text{H}$  NMR ( $\text{CDCl}_3$ , 500 MHz):  $\delta$  8.46-8.44 (m, 1H), 7.64 (s, 1H), 7.37-7.32 (m, 3 H), 7.09 (d,  $J = 1.3$  Hz, 1H), 6.95 (d,  $J = 1.3$  Hz, 1H), 5.28 (d,  $J = 6.5$  Hz, 1H), 5.19 (d,  $J = 6.5$  Hz, 1H), 4.75 (dd,  $J = 13.8, 6.8$  Hz, 2H), 3.84 (s, 3H), 3.78 (m, 1H), 3.51 (s, 3H), 3.47 (m, 1H), 3.41 (s, 3H), 2.55 (td,  $J = 11.3$  Hz, 2.5 Hz, 1H), 2.26-2.20 (m, 1H), 1.95 (m, 1H), 1.59 (td,  $J = 11.6$  Hz, 2.3 Hz, 1H), 1.52-1.42 (m, 4H), 1.21-1.12 (m, 2H), 1.07 (s, 3H)

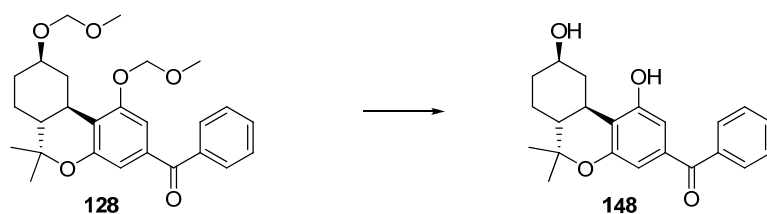
$^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 126 MHz):  $\delta$  189.9, 156.3, 154.4, 140.3, 138.0, 137.5, 127.3, 123.5, 122.8, 122.6, 117.2, 115.2, 112.2, 109.5, 105.8, 94.8, 94.5, 75.6, 56.4, 55.2, 48.6, 36.4, 34.2, 33.5, 33.1, 27.7, 26.1, 18.8

IR (thin film,  $\text{cm}^{-1}$ ): 3114, 3053, 2935, 2824, 1623, 1565, 1525, 1464, 1369, 1215, 1057

HR EI+ Calculated for  $\text{C}_{29}\text{H}_{35}\text{NO}_6$ : 493.2464, found: 493.2446 (3.6 ppm error)

EI+ ( $m/z$ ): 493 ( $\text{M}^+$ , 64), 387 (86), 344 (29), 207 (61), 158 (100), 144 (83)

$[\alpha]_{\text{D}}^{23}$  -84 ( $c$  0.016, EtOAc)



### General Experimental for the Removal of the Methoxymethyl ether Group

TMSBr was prepared by adding Br<sub>2</sub> (100  $\mu$ L, 1.95 mmol) dropwise to a solution of hexamethyldisilane (420  $\mu$ L, 2.05 mmol) in 5 mL of CH<sub>2</sub>Cl<sub>2</sub> at -78 °C under N<sub>2</sub>, stirred for 5 min then warmed to room temperature where the reaction mixture changed color from orange to clear and colorless (sometimes the solution has a slight orange or yellow color to it but it does not affect the yield of the following reaction).

To ketone **128** (33 mg, 0.075 mmol) in 1 mL of CH<sub>2</sub>Cl<sub>2</sub> at -40 °C was added a 0.35 M solution of TMSBr in CH<sub>2</sub>Cl<sub>2</sub> (0.43 mL, 0.15 mmol) via syringe and stirred for 45 min. Additional TMSBr (0.43 mL, 0.15 mmol) was added at -40 °C and stirred for 45 min. The reaction mixture was then warmed to 0 °C followed by the addition of TMSBr (0.43 mL, 0.15 mmol) and stirred for 1 h. The reaction was quenched with saturated NaHCO<sub>3</sub>, extracted with EtOAc, washed with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude product was then purified *via* flash column chromatography on silica gel eluting with 2.5% then 5% EtOH(abs.)/ CH<sub>2</sub>Cl<sub>2</sub> to afford alcohol **148** (16 mg, 61% yield) as a tan glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 254 nm) 3.95 min and 98.4% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  7.75 (d,  $J$  = 7.0 Hz, 2H), 7.62 (t,  $J$  = 7.3 Hz, 1H), 7.51 (t,  $J$  = 7.8 Hz, 2H), 6.73 (d,  $J$  = 1.5 Hz, 1H), 6.61 (d,  $J$  = 1.5 Hz, 1H), 3.78 (m, 1H), 3.57 (m, 1H), 2.55 (td,  $J$  = 11.3 Hz, 2.3 Hz, 1H), 2.14 (m, 1H), 1.93 (m, 1H), 1.52 (m, 1H), 1.44-1.36 (m, 4H), 1.22 (m, 1H), 1.07 (s, 3H), 0.99 (m, 1H)

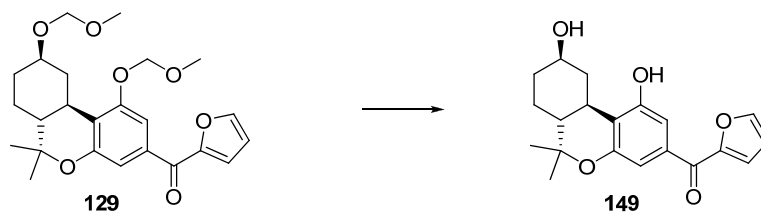
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  198.4, 158.2, 156.2, 139.1, 137.7, 133.5, 130.9, 129.3, 118.8, 112.0, 109.3, 78.4, 71.3, 50.0, 39.4, 36.6, 35.4, 28.1, 27.2, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3253(br), 2931, 2861, 1641, 1568, 1417, 1056

HR EI+ Mass Spec. Calculated for  $\text{C}_{22}\text{H}_{24}\text{O}_4$ : 352.1675, found: 352.1675 (0.0 ppm error)

EI+ ( $m/z$ ): 352 ( $\text{M}^+$ , 61), 334 (32), 291 (55), 265 (29), 105 (100), 91 (4), 77 (32)

$[\alpha]_{\text{D}}^{23}$  -147 ( $c$  0.006, EtOAc)



Prepared in 42% yield as a beige glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 254 nm) 4.00 min and 95.3% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  7.88 (d,  $J$  = 1.0 Hz, 1H), 7.31 (d,  $J$  = 3.5 Hz, 1H), 6.89 (d,  $J$  = 1.8 Hz, 1H), 6.85 (d,  $J$  = 1.8 Hz, 1H), 6.69 (dd,  $J$  = 3.5 Hz, 2.0 Hz, 1H), 3.77 (m, 1H), 3.56 (m, 1H), 2.55 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.14 (m, 1H), 1.93 (m, 1H), 1.51 (td,  $J$  = 11.5 Hz, 2.3 Hz, 1H), 1.44-1.36 (m, 4H), 1.22 (m, 1H), 1.07 (s, 3H), 0.99 (m, 1H)

$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  183.9, 158.1, 156.4, 153.3, 149.2, 137.4, 122.3, 118.9, 113.4, 111.2, 108.4, 78.4, 71.3, 50.0, 39.4, 36.6, 35.4, 28.1, 27.2, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3218(br), 2931, 2863, 1632, 1563, 1463, 1341, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{22}\text{O}_5$ : 342.1467, found: 342.1469 (0.6 ppm error)

EI+ ( $m/z$ ): 342 ( $\text{M}^+$ , 74), 324 (66), 281 (69), 255 (39), 149 (74), 95 (100)

$[\alpha]_{\text{D}}^{23}$  -79 ( $c$  0.005, EtOAc)



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Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 3.85 min and 98.4% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.11 (dd,  $J$  = 1.3 Hz, 0.8 Hz, 1H), 7.65-7.64 (m, 1H), 6.86 (dd,  $J$  = 1.8 Hz, 0.8 Hz, 1H), 6.80 (d,  $J$  = 1.8 Hz, 1H), 6.73 (d,  $J$  = 1.8 Hz, 1H), 3.77 (m, 1H), 3.55 (m, 1H), 2.54 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.16-2.12 (m, 1H), 1.93 (m, 1H), 1.51 (td,  $J$  = 11.6 Hz, 2.2 Hz, 1H), 1.40 (m, 4H), 1.24 (m, 1H), 1.07 (s, 3H), 0.98 (m, 1H)

$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  191.0, 158.2, 156.5, 150.5, 145.6, 139.0, 127.5, 118.7, 110.9, 110.7, 108.1, 78.4, 71.3, 50.0, 39.4, 36.6, 35.4, 28.1, 27.2, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3367 (br), 2932, 2870, 1734, 1717, 1635, 1571, 1508, 1419, 1340, 1047

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{22}\text{O}_5$ : 342.1467, found: 342.1470 (0.9 ppm error)

EI+ ( $m/z$ ): 342 ( $\text{M}^+$ , 31), 324 (71), 281 (32), 269 (29), 255 (24), 217 (24), 129 (18), 95 (100), 84 (80)

$[\alpha]_{\text{D}}^{23}$  -103 ( $c$  0.004, EtOAc)



Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 4.19 min and 97.4% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  7.80 (d,  $J$  = 8.0 Hz, 1H), 7.66-7.64 (m, 2H), 7.54 (ddd,  $J$  = 8.8 Hz, 7.5 Hz, 1.0 Hz, 1H), 7.36 (t,  $J$  = 7.5 Hz, 1H), 6.98 (d,  $J$  = 1.8 Hz, 1H), 6.95 (d,  $J$  = 1.8 Hz, 1H), 3.81-3.75 (m, 1H), 3.57 (m, 1H), 2.57 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.15 (m, 1H), 1.53 (td,  $J$  = 11.6 Hz, 2.2 Hz, 1H), 1.45-1.37 (m, 4H), 1.24 (m, 1H), 1.09 (s, 3H), 1.01 (m, 1H)

$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  185.5, 158.2, 157.4, 156.5, 153.4, 137.3, 129.7, 128.4, 125.2, 124.7, 119.4, 117.9, 113.1, 111.4, 108.6, 78.5, 71.3, 50.0, 39.4, 36.6, 35.4, 28.1, 27.2, 19.2

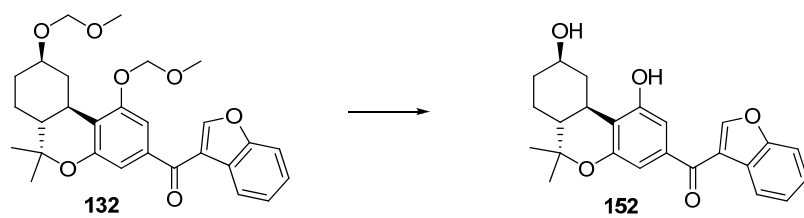
IR (thin film,  $\text{cm}^{-1}$ ): 3420 (br), 1636, 1572, 1544, 1419, 1363, 1339, 1055

HR EI+ Mass Spec. Calculated for  $\text{C}_{24}\text{H}_{24}\text{O}_5$ : 392.1624, found: 392.1621 (0.8 ppm error)

EI+ ( $m/z$ ): 392 ( $\text{M}^+$ , 32), 331 (10), 310 (14), 279 (25), 167 (26), 149 (100), 129 (13), 112 (10), 71 (24)

$[\alpha]_D^{23}$  -100 ( $c$  0.009, EtOAc)





Prepared in 66% yield as a beige glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 254 nm) 4.17 min and 97.7% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.36 (s, 1H), 8.15 (dd,  $J$  = 7.8 Hz, 1.3 Hz, 1H), 7.60 (d,  $J$  = 7.5 Hz, 1H), 7.43 (td,  $J$  = 7.6 Hz, 1.6 Hz, 1H), 7.39 (td,  $J$  = 7.6 Hz, 1.2 Hz, 1H), 6.84 (d,  $J$  = 2.0 Hz, 1H), 6.78 (d,  $J$  = 2.0 Hz, 1H), 3.78 (m, 1H), 3.57 (m, 1H), 2.56 (td,  $J$  = 11.4 Hz, 2.3 Hz, 1H), 2.16 (m, 1H), 1.93 (m, 1H), 1.52 (td,  $J$  = 11.6 Hz, 2.2 Hz, 1H), 1.45-1.36 (m, 4H), 1.23 (m, 1H), 1.08 (s, 3H), 1.00 (m, 1H)

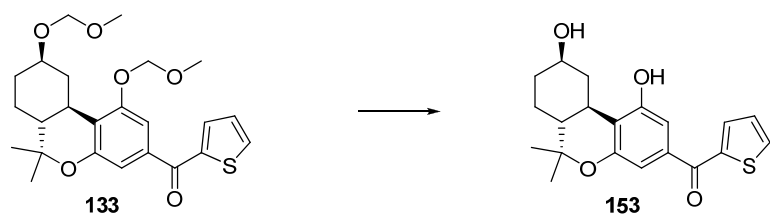
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  191.7, 158.3, 157.0, 156.6, 154.5, 139.5, 126.9, 126.5, 125.5, 123.6, 122.0, 118.6, 112.5, 110.7, 108.1, 78.5, 71.3, 50.0, 39.5, 36.6, 35.4, 28.1, 27.2, 19.2

IR (thin film,  $\text{cm}^{-1}$ ): 3405 (br), 2979, 2937, 2871, 1735, 1641, 1573, 1547, 1419, 1373, 1277, 1247, 1137, 1048

HR EI+ Mass Spec. Calculated for  $\text{C}_{24}\text{H}_{24}\text{O}_5$ : 392.1624, found: 392.1617 (1.8 ppm error)

EI+ ( $m/z$ ): ( $\text{M}^+$ , 100), 331 (20), 145 (46)

$[\alpha]_{\text{D}}^{23}$  -121 ( $c$  0.016, EtOAc)



Prepared in 51% yield as a beige glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 7.63 min and 98.8% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  7.89 (dd,  $J$  = 5.3 Hz, 1.3 Hz, 1H), 7.74 (dd,  $J$  = 3.8 Hz, 1.3 Hz, 1H), 7.22 (dd,  $J$  = 5.0 Hz, 4.0 Hz, 1H), 6.79 (d,  $J$  = 2.0 Hz, 1H), 6.72 (d,  $J$  = 2.0 Hz, 1H), 3.78 (m, 1H), 3.57 (m, 1H), 2.55 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.14 (m, 1H), 1.93 (m, 1H), 1.52 (td,  $J$  = 11.8 Hz, 2.3 Hz, 1H), 1.43-1.36 (m, 4H), 1.22 (m, 1H), 1.07 (s, 3H), 1.00 (m, 1H)

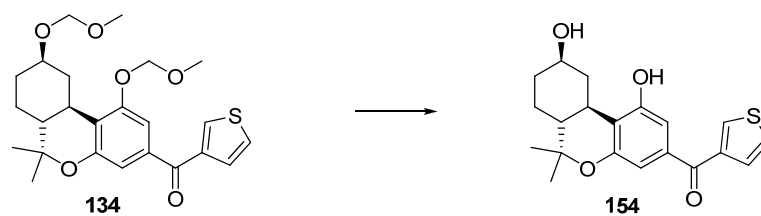
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  189.6, 158.3, 156.3, 144.1, 138.3, 136.4, 135.8, 129.2, 118.5, 110.9, 108.5, 78.4, 71.3, 50.0, 39.5, 36.6, 35.4, 28.1, 27.2, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3379(br), 2981, 2934, 2856, 1734, 1635, 1570, 1508, 1419, 1341, 1246, 1055

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{22}\text{O}_4\text{S}$ : 358.1239, found: 358.1245 (1.7 ppm error)

EI+ ( $m/z$ ): 358 ( $\text{M}^+$ , 6), 207 (57), 149 (70), 122 (20), 107 (29), 101 (100), 98 (35), 85 (25), 71 (46)

$[\alpha]_{\text{D}}^{23}$  -48 ( $c$  0.005, EtOAc)



Prepared in 40% yield as white needles.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 260 nm) 7.73 min and 96.0% chemical purity.

mp: >230 °C

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.07 (app t,  $J$  = 2.0 Hz, 1H), 7.53 (s, 1H), 7.52 (s, 1H), 6.77 (d,  $J$  = 1.5 Hz, 1H), 6.69 (d,  $J$  = 1.5 Hz, 1H), 3.79-3.73 (m, 1H), 3.56 (m, 1H), 2.54 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.13 (m, 1H), 1.92 (m, 1H), 1.50 (td,  $J$  = 11.6 Hz, 2.2 Hz, 1H), 1.44-1.33 (m, 4H), 1.22 (m, 1H), 1.06 (s, 3H), 0.99 (m, 1H)

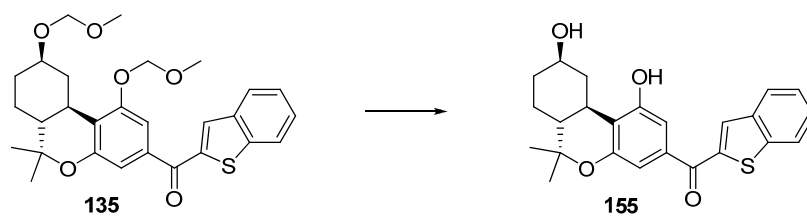
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  191.7, 158.1, 156.3, 142.3, 138.8, 135.6, 129.3, 127.6, 118.6, 111.4, 108.7, 78.4, 71.3, 50.0, 39.5, 36.6, 35.4, 28.1, 27.2, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3378(br), 2932, 2857, 1652, 1634, 1574, 1511, 1419, 1341, 1246, 1178, 1136, 1055

HR EI+ Mass Spec. Calculated for  $\text{C}_{20}\text{H}_{22}\text{O}_4\text{S}$ : 358.1239, found: 358.1248 (2.5 ppm error)

EI+ ( $m/z$ ): 358 ( $\text{M}^+$ , 89), 297 (68), 271 (37), 149 (51), 111 (100)

$[\alpha]_{\text{D}}^{23}$  -106 ( $c$  0.010, EtOAc)



Prepared in 65% yield as a tan oil.

Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 212 nm) 4.40 min and 98.8% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.00 (s, 1H), 7.97 (d,  $J$  = 9.3 Hz, 1H), 7.95 (d,  $J$  = 9.3 Hz, 1H), 7.51 (ddd,  $J$  = 9.5 Hz, 7.5 Hz, 1.0 Hz, 1H), 7.44 (ddd,  $J$  = 9.5 Hz, 7.5 Hz, 1.0 Hz, 1H), 6.85 (d,  $J$  = 1.5 Hz, 1H), 6.79 (d,  $J$  = 1.5 Hz, 1H), 3.78 (m, 1H), 3.58 (m, 1H), 2.57 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.15 (m, 1H), 1.94 (m, 1H), 1.53 (td,  $J$  = 11.5 Hz, 2.3 Hz, 1H), 1.45-1.37 (m, 4H), 1.24 (m, 1H), 1.09 (s, 3H), 1.01 (m, 1H)

$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  190.9, 158.2, 156.4, 143.9, 140.6, 138.0, 133.8, 128.8, 127.4, 126.2, 123.8, 118.8, 111.1, 108.5, 78.5, 71.3, 50.0, 39.4, 36.6, 35.4, 28.1, 27.2, 19.2

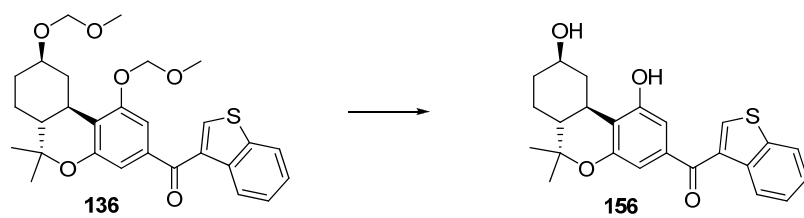
IR (thin film,  $\text{cm}^{-1}$ ): 3420 (br), 2978, 2933, 2869, 1734, 1716, 1634, 1571, 1511, 1418, 1343, 1265, 1047

HR EI+ Mass Spec. Calculated for  $\text{C}_{24}\text{H}_{24}\text{O}_4\text{S}$ : 408.1395, found: 408.1390 (1.2 ppm error)

EI+ ( $m/z$ ): 408 ( $\text{M}^+$ , 25), 390 (37), 347 (24), 167 (19), 161 (61), 149 (100), 83 (21), 71 (21), 69 (21)

$[\alpha]_{\text{D}}^{23}$  -104 ( $c$  0.007, EtOAc)





Prepared in 73% yield as a tan oil.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 212 nm) 8.47 min and 98.1% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.41 (d,  $J = 7.8$  Hz, 1H), 8.23 (s, 1H), 7.97 (d,  $J = 7.8$  Hz, 1H), 7.50-7.43 (m, 2H), 6.81 (br s, 1H), 6.72 (d,  $J = 1.5$  Hz, 1H), 3.78 (m, 1H), 3.57 (m, 1H), 2.56 (td,  $J = 11.4$  Hz, 1.7 Hz, 1H), 2.15 (m, 1H), 1.93 (m, 1H), 1.52 (td,  $J = 11.5$  Hz, 1.8 Hz, 1H), 1.44-1.36 (m, 4H), 1.22 (m, 1H), 1.07 (s, 3H), 1.00 (m, 1H)

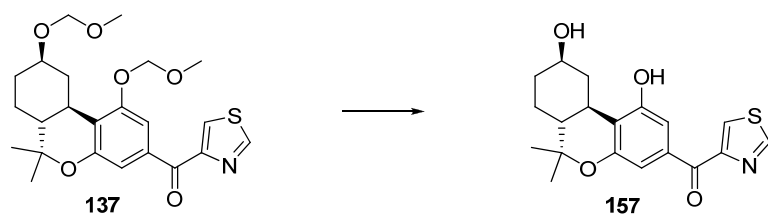
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  192.4, 158.2, 156.4, 141.5, 140.1, 139.5, 138.7, 135.6, 118.6, 111.5, 108.8, 78.4, 71.3, 50.0, 39.5, 36.6, 35.4, 28.1, 27.2, 19.2

IR (thin film,  $\text{cm}^{-1}$ ): 3395 (br), 2976, 2931, 2869, 1734, 1637, 1571, 1420, 1199, 1138, 1047

HR EI+ Mass Spec. Calculated for  $\text{C}_{24}\text{H}_{24}\text{O}_4\text{S}$ : 408.1395, found: 408.1394 (0.3 ppm error)

EI+ ( $m/z$ ): 408 ( $\text{M}^+$ , 37), 347 (23), 281 (65), 269 (35), 267 (30), 221 (36), 207 (100), 161 (50), 72 (59)

$[\alpha]_{\text{D}}^{23}$  -120 ( $c$  0.003, MeOH)



Prepared in 65% yield as a fluffy tan solid.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 212 nm) 8.07 min and 98.1% chemical purity.

mp: >220 °C (dec.);

<sup>1</sup>H NMR (MeOH-*d*<sub>4</sub>, 500 MHz): δ 9.09 (d, *J* = 2.0 Hz, 1H), 8.36 (d, *J* = 2.0 Hz, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.96 (d, *J* = 1.5 Hz, 1H), 3.79-3.73 (m, 1H), 3.56 (m, 1H), 2.53 (td, *J* = 11.33 Hz, 2.3 Hz, 1H), 2.12 (m, 1H), 1.90 (m, 1H), 1.49 (td, *J* = 11.3 Hz, 2.3 Hz, 1H), 1.42-1.34 (m, 4H), 1.20 (m, 1H), 1.05 (s, 3H), 0.97 (m, 1H)

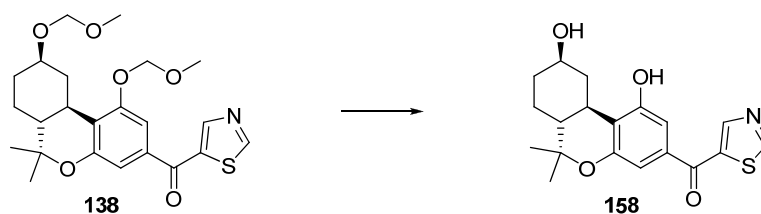
<sup>13</sup>C NMR (MeOH-*d*<sub>4</sub>, 126 MHz): δ 188.5, 158.0, 156.3, 155.8, 155.7, 137.5, 129.8, 119.3, 112.3, 109.2, 78.4, 71.3, 50.0, 39.4, 36.5, 35.4, 28.1, 27.1, 19.2

IR (thin film, cm<sup>-1</sup>): 3392(br), 2925, 2854, 1720, 1652, 1460, 1419, 1375, 1274, 1135, 1055

HR EI+ Mass Spec. Calculated for C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub>S: 359.1191, found: 359.1185 (1.7 ppm error)

EI+(*m/z*): 359 M<sup>+</sup>, 24), 341 (89), 298 (50), 272 (43), 112 (100)

[α]<sub>D</sub><sup>23</sup> -135 (*c* 0.010, MeOH)



Prepared in 66% yield as a brown oil.

Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 254 nm) 4.30 min and 96.8% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  9.29 (s, 1H), 8.41 (s, 1H), 6.84 (d,  $J = 1.5$  Hz, 1H), 6.78 (d,  $J = 1.5$  Hz, 1H), 3.78 (m, 1H), 3.56 (m, 1H), 2.56 (td,  $J = 11.3$  Hz, 2.0 Hz, 1H), 2.15 (m, 1H), 1.94 (m, 1H), 1.53 (td,  $J = 11.6$  Hz, 1.8 Hz, 1H), 1.45-1.36 (m, 4H), 1.23 (m, 1H), 1.08 (s, 3H), 1.00 (m, 1H)

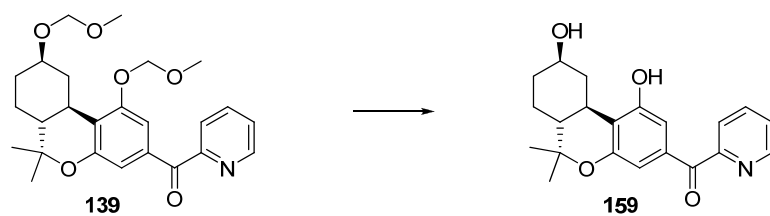
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  188.1, 161.5, 158.4, 156.6, 149.6, 140.5, 137.8, 119.4, 111.0, 108.3, 78.6, 71.3, 49.9, 39.4, 36.6, 35.4, 28.1, 27.1, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3397 (br), 2977, 2932, 2869, 1732, 1637, 1572, 1505, 1419, 1342, 1242, 1055

HR EI+ Mass Spec. Calculated for  $\text{C}_{19}\text{H}_{21}\text{NO}_4\text{S}$ : 359.1191, found: 359.1181 (2.8 ppm error)

EI+ ( $m/z$ ): 359 ( $\text{M}^+$ , 5), 337 (42), 253 (24), 199 (100), 91 (17), 77 (15), 68 (13)

$[\alpha]_{\text{D}}^{23}$  -98 ( $c$  0.006, EtOAc)



Prepared in 66% yield as a brown glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 254 nm) 4.67 min and 97.4% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.66-8.64 (m, 1H), 8.01 (dt,  $J = 7.6$  Hz, 1.7 Hz, 1H), 7.86 (d,  $J = 7.6$  Hz, 1H), 7.61 (ddd,  $J = 7.5$  Hz, 5.0 Hz, 1.0 Hz, 1H), 6.91 (d,  $J = 1.5$  Hz, 1H), 6.79 (d,  $J = 1.5$  Hz, 1H), 3.76 (m, 1H), 3.56 (m, 1H), 2.54 (td,  $J = 11.1$  Hz, 2.2 Hz, 1H), 2.14 (m, 1H), 1.92 (m, 1H), 1.50 (td,  $J = 11.6$  Hz, 2.0 Hz, 1H), 1.43-1.35 (m, 4H), 1.21 (m, 1H), 1.06 (s, 3H), 0.98 (m, 1H)

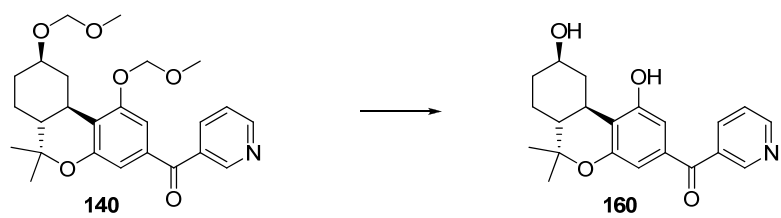
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  195.0, 158.0, 156.6, 156.2, 149.6, 138.9, 136.3, 127.6, 125.6, 119.6, 113.0, 109.6, 78.4, 71.3, 50.0, 39.4, 36.6, 35.4, 28.1, 27.1, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3272(br), 2978, 2935, 2870, 1735, 1660, 1571, 1419, 1341, 1275, 1141, 1047

HR EI+ Mass Spec. Calculated for  $\text{C}_{21}\text{H}_{23}\text{NO}_4$ : 353.1627, found: 353.1616 (3.1 ppm error)

EI+ ( $m/z$ ): 353 ( $\text{M}^+$ , 78), 335 (41), 292 (55), 266 (30), 106 (58), 78 (100)

$[\alpha]_{\text{D}}^{23}$  -118 ( $c$  0.004, EtOAc)



Prepared in 73% yield as a brown glass.



Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 212 nm) 7.03 min and 97.7% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.85 (s, 1H), 8.73 (d,  $J$  = 4.0 Hz, 1H), 8.16-8.13 (m, 1H), 7.57 (dd,  $J$  = 7.8 Hz, 4.8 Hz, 1H), 6.74 (d,  $J$  = 1.8 Hz, 1H), 6.61 (d,  $J$  = 1.8 Hz, 1H), 3.76 (m, 1H), 3.55 (m, 1H), 2.53 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.12 (m, 1H), 1.90 (m, 1H), 1.49 (td,  $J$  = 11.6 Hz, 2.2 Hz, 1H), 1.43-1.34 (m, 4H), 1.19 (m, 1H), 1.04 (s, 3H), 0.98 (m, 1H)

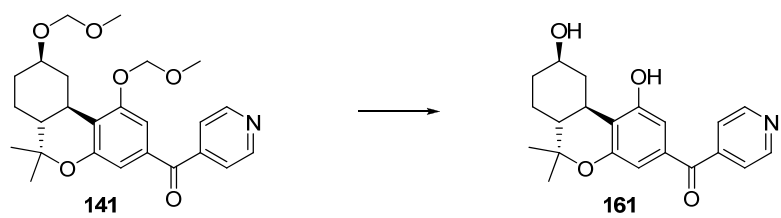
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  195.6, 158.5, 156.4, 153.0, 150.9, 139.0, 136.8, 135.3, 125.0, 119.6, 112.0, 109.2, 78.5, 71.2, 49.9, 39.3, 36.5, 35.4, 28.1, 27.1, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3235(br), 2977, 2934, 2869, 1735, 1657, 1572, 1418, 1342, 1263, 1140, 1057

HR EI+ Mass Spec. Calculated for  $\text{C}_{21}\text{H}_{23}\text{NO}_4$ : 353.1627, found: 353.1634 (2.0 ppm error)

EI+ ( $m/z$ ): 353 ( $\text{M}^+$ , 24), 207 (100), 149 (30), 101 (28)

$[\alpha]_{\text{D}}^{22}$  -143 ( $c$  0.010, MeOH)



Prepared in 69% yield as a brown glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 7.00 min and 98.4% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.71 (d,  $J$  = 4.8 Hz, 2H), 7.62 (d,  $J$  = 4.8 Hz, 2H), 6.76 (d,  $J$  = 1.8 Hz, 1H), 6.62 (d,  $J$  = 1.8 Hz, 1H), 3.79-3.71 (m, 1H), 3.54 (m, 1H), 2.53 (td,  $J$  = 11.3 Hz, 2.3 Hz, 1H), 2.12 (m, 1H), 1.90 (m, 1H), 1.48 (td,  $J$  = 11.5 Hz, 2.2 Hz, 1H), 1.42-1.33 (m, 4H), 1.20 (m, 1H), 1.03 (s, 3H), 0.96 (m, 1H)

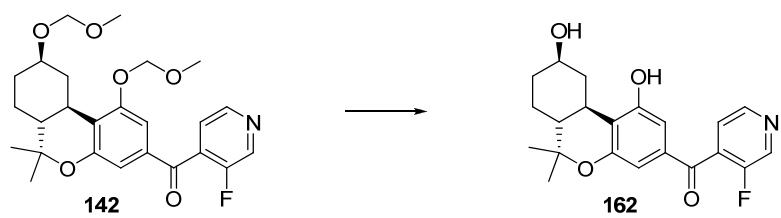
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  195.8, 158.6, 156.5, 150.7, 147.2, 136.0, 124.4, 120.0, 112.1, 109.2, 78.5, 71.2, 49.9, 39.3, 36.5, 35.4, 28.1, 27.1, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3228(br), 2933, 2866, 1661, 1573, 1419, 1342, 1141, 1059

HR EI+ Mass Spec. Calculated for  $\text{C}_{21}\text{H}_{23}\text{NO}_4$ : 353.1627, found: 353.1611 (4.5 ppm error)

EI+ ( $m/z$ ): 353 ( $\text{M}^+$ , 43), 335 (22), 292 (38), 279 (21), 207 (81), 165 (35), 149 (100), 106 (39), 69 (48)

$[\alpha]_{\text{D}}^{23}$  -129 ( $c$  0.010, MeOH)



Prepared in 67% yield as a yellow oil.

Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 280 nm) 4.02 min and 98.6% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.63 (s, 1H), 8.55 (d,  $J = 4.5$  Hz, 1H), 7.49 (t,  $J = 5.8$  Hz, 1H), 6.78 (d,  $J = 1.5$  Hz, 1H), 6.62 (d,  $J = 1.5$  Hz, 1H), 3.76 (m, 1H), 3.53 (m, 1H), 2.54 (td,  $J = 11.3$  Hz, 2.2 Hz, 1H), 2.15-2.10 (m, 1H), 1.91 (m, 1H), 1.50 (td,  $J = 11.5$  Hz, 2.2 Hz, 1H), 1.43-1.34 (m, 4H), 1.21 (m, 1H), 1.05 (s, 3H), 0.97 (m, 1H)

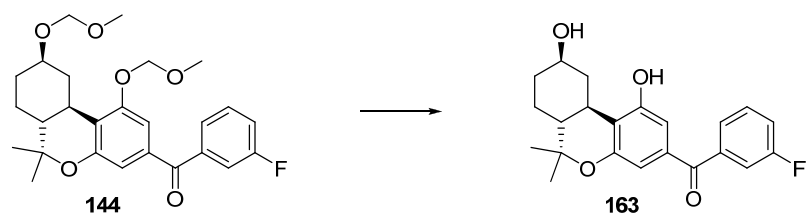
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  191.9, 157.7 (d,  $J_{\text{CF}} = 233.1$  Hz), 146.9 (d,  $J_{\text{CF}} = 4.7$  Hz), 139.8 (d,  $J_{\text{CF}} = 24.6$  Hz), 136.3, 136.2, 136.1, 124.7, 121.0, 111.9, 108.4, 78.6, 71.2, 49.8, 39.2, 36.5, 35.5, 28.0, 27.1, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3420 (br), 2979, 2935, 2870, 1669, 1574, 1421, 1342, 1056

HR EI+ Mass Spec. Calculated for  $\text{C}_{21}\text{H}_{22}\text{FNO}_4$ : 371.1533, found: 371.1539 (1.6 ppm error)

EI+ ( $m/z$ ): 371 ( $\text{M}^+$ , 100), 353 (60), 284 (22), 270 (17), 199 (44), 124 (67)

$[\alpha]_{\text{D}}^{23}$  -110 ( $c$  0.015, EtOAc)



Prepared in 63% yield as a light brown glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 254 nm) 3.80 min and 97.7% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  7.56-7.50 (m, 2H), 7.47-7.44 (m, 1H), 7.38-7.34 (m, 1H), 6.74 (d,  $J = 1.8$  Hz, 1H), 6.62 (d,  $J = 1.8$  Hz, 1H), 3.77 (m, 1H), 3.56 (m, 1H), 2.55 (td,  $J = 11.3$  Hz, 2.2 Hz, 1H), 2.14 (m, 1H), 1.92 (m, 1H), 1.51 (td,  $J = 11.6$  Hz, 2.2 Hz, 1H), 1.44-1.36 (m, 4H), 1.22 (m, 1H), 1.06 (s, 3H), 1.00 (m, 1H)

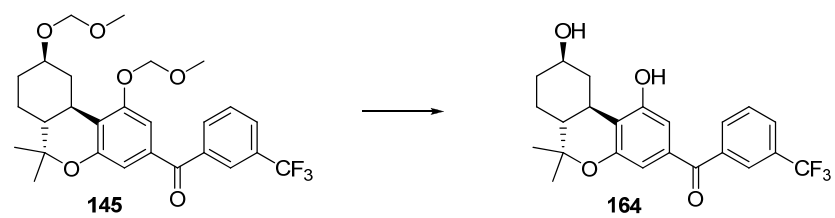
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  196.6, 164.8, 162.9, 157.2 (d,  $J_{CF} = 230.4$  Hz), 141.3 (d,  $J_{CF} = 6.3$  Hz), 131.3 (d,  $J_{CF} = 7.8$  Hz), 126.9 (d,  $J_{CF} = 2.1$  Hz), 120.2 (d,  $J_{CF} = 21.5$  Hz), 117.1 (d,  $J_{CF} = 22.4$  Hz), 112.1, 109.1, 78.5, 71.3, 50.0, 39.4, 36.5, 35.4, 28.1, 27.1, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3399 (br), 2979, 2936, 2870, 1708, 1653, 1573, 1419, 1340, 1265, 1139, 1047

HR EI+ Mass Spec. Calculated for  $\text{C}_{22}\text{H}_{23}\text{FO}_4$ : 370.1580, found: 370.1594 (3.8 ppm error)

EI+( $m/z$ ): 370 ( $\text{M}^+$ , 42), 352 (50), 337 (17), 309 (55), 283 (32), 123 (100), 95 (26), 69 (13)

$[\alpha]_D^{23}$  -111 ( $c$  0.015, EtOAc)



Prepared in 70% yield as a light brown glass.



Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 254 nm) 3.68 min and 97.0% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.02-7.97 (m, 2H), 7.92 (d,  $J$  = 7.8 Hz, 1H), 7.72 (t,  $J$  = 7.8 Hz, 1H), 6.74 (d,  $J$  = 1.8 Hz, 1H), 6.63 (d,  $J$  = 1.8 Hz, 1H), 3.81-3.74 (m, 1H), 3.56 (m, 1H), 2.56 (td,  $J$  = 11.3 Hz, 2.2 Hz, 1H), 2.14 (m, 1H), 1.93 (m, 1H), 1.52 (td,  $J$  = 11.6 Hz, 2.0 Hz, 1H), 1.45-1.36 (m, 4H), 1.23 (m, 1H), 1.07 (s, 3H), 1.00 (m, 1H)

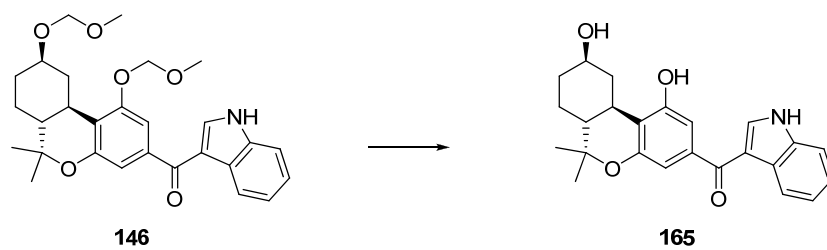
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  196.4, 158.2, 156.4, 140.0, 137.0, 134.4, 131.8 (q,  $J_{\text{CF}}$  = 32.7 Hz), 130.4, 129.8 (q,  $J_{\text{CF}}$  = 3.0 Hz), 127.1 (q,  $J_{\text{CF}}$  = 3.5 Hz), 125.3 (q,  $J_{\text{CF}}$  = 271.7 Hz), 119.3, 112.0, 109.1, 78.5, 71.3, 50.0, 39.4, 36.6, 35.4, 28.1, 27.2, 19.1

IR (thin film,  $\text{cm}^{-1}$ ): 3399 (br), 2979, 2938, 2871, 1652, 1573, 1420, 1345, 1328, 1234, 1170, 1131, 1056

HR EI+ Mass Spec. Calculated for  $\text{C}_{23}\text{H}_{23}\text{F}_3\text{O}_4$ : 420.1548, found: 420.1551 (0.7 ppm error)

EI+ ( $m/z$ ): 420 ( $\text{M}^+$ , 78), 402 (16), 387 (21), 359 (63), 333 (28), 173 (100), 145 (33), 69 (16)

$[\alpha]_{\text{D}}^{23}$  -105 ( $c$  0.014, EtOAc)



Prepared in 82% yield as a tan solid.

Chiral HPLC (0.46 cm x 25 cm Chiralcel OD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 254 nm) 3.75 min and 98.1% chemical purity.

mp: 158-161°C (dec.)

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.26 (dd,  $J$  = 6.8 Hz, 1.3 Hz, 1H), 7.86 (s, 1H), 7.48 (dd,  $J$  = 6.8 Hz, 1.3 Hz, 1H), 7.29-7.22 (m, 2H), 6.75 (d,  $J$  = 2.0 Hz, 1H), 6.68 (d,  $J$  = 2.0 Hz, 1H), 3.79 (m, 1H), 3.58 (m, 1H), 2.56 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.15 (m, 1H), 1.93 (m, 1H), 1.52 (td,  $J$  = 11.8 Hz, 2.3 Hz, 1H), 1.45-1.36 (m, 4H), 1.23 (m, 1H), 1.09 (s, 3H), 1.01 (m, 1H)

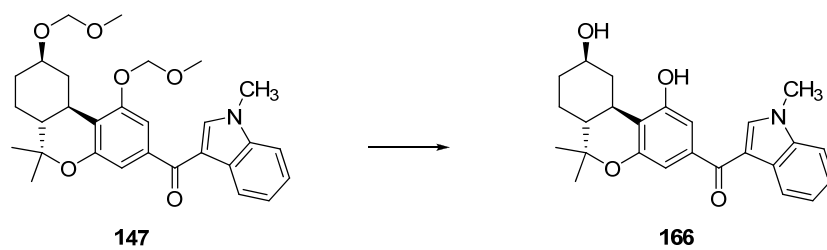
$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  193.6, 158.0, 156.2, 141.2, 138.5, 137.2, 127.8, 124.6, 123.3, 122.9, 117.1, 117.0, 112.9, 110.6, 108.3, 78.3, 71.3, 50.1, 39.6, 36.6, 35.3, 28.1, 27.2, 19.2

IR (thin film,  $\text{cm}^{-1}$ ): 3250(br), 2930, 2867, 1625, 1599, 1371, 1056

HR EI+ Mass Spec. Calculated for  $\text{C}_{24}\text{H}_{25}\text{NO}_4$ : 391.1784, found: 391.1779 (1.3 ppm error)

EI+ ( $m/z$ ): 391 ( $\text{M}^+$ , 5), 373 (29), 352 (53), 334 (50), 291 (61), 265 (38), 149 (90), 105 (100)

$[\alpha]_{\text{D}}^{23}$  -108 ( $c$  0.006, EtOAc)



Prepared in 63% yield as a beige glass.

Chiral HPLC (0.46 cm x 25 cm Chiralcel AD-H, 50% 2-propanol in hexanes, 1 mL/min, UV detection at 212 nm) 10.20 min and 96.9% chemical purity.

$^1\text{H}$  NMR (MeOH- $d_4$ , 500 MHz):  $\delta$  8.26 (d,  $J$  = 8.0 Hz, 1H), 7.81 (s, 1H), 7.45 (d,  $J$  = 8.0 Hz, 1H), 7.30 (t,  $J$  = 7.4 Hz, 1H), 7.26 (t,  $J$  = 7.4 Hz, 1H), 6.73 (d,  $J$  = 1.8 Hz, 1H), 6.65 (d,  $J$  = 1.8 Hz, 1H), 3.84 (s, 3H), 3.76 (m, 1H), 3.57 (m, 1H), 2.53 (td,  $J$  = 11.3 Hz, 2.5 Hz, 1H), 2.12 (m, 1H), 1.90 (m, 1H), 1.48 (td,  $J$  = 11.6 Hz, 2.2 Hz, 1H), 1.42-1.34 (m, 4H), 1.19 (m, 1H), 1.06 (s, 3H), 0.98 (m, 1H)

$^{13}\text{C}$  NMR (MeOH- $d_4$ , 126 MHz):  $\delta$  193.1, 158.3, 156.2, 141.1, 140.9, 139.2, 128.4, 124.6, 123.6, 123.2, 117.1, 115.9, 111.2, 110.4, 108.4, 78.3, 71.3, 50.1, 39.6, 36.6, 35.3, 33.7, 28.1, 27.2, 19.2

IR (thin film,  $\text{cm}^{-1}$ ): 3358(br), 2978, 2935, 2870, 1732, 1605, 1567, 1523, 1464, 1369, 1055

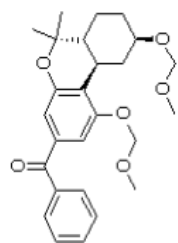
HR EI+ Mass Spec. Calculated for  $\text{C}_{25}\text{H}_{27}\text{NO}_4$ : 405.1940, found: 405.1950 (2.5 ppm error)

EI+( $m/z$ ): 405 ( $\text{M}^+$ , 23), 354 (42), 291 (35), 207 (38), 158 (76), 129 (78), 115 (45), 105 (64), 91 (66), 73 (100)

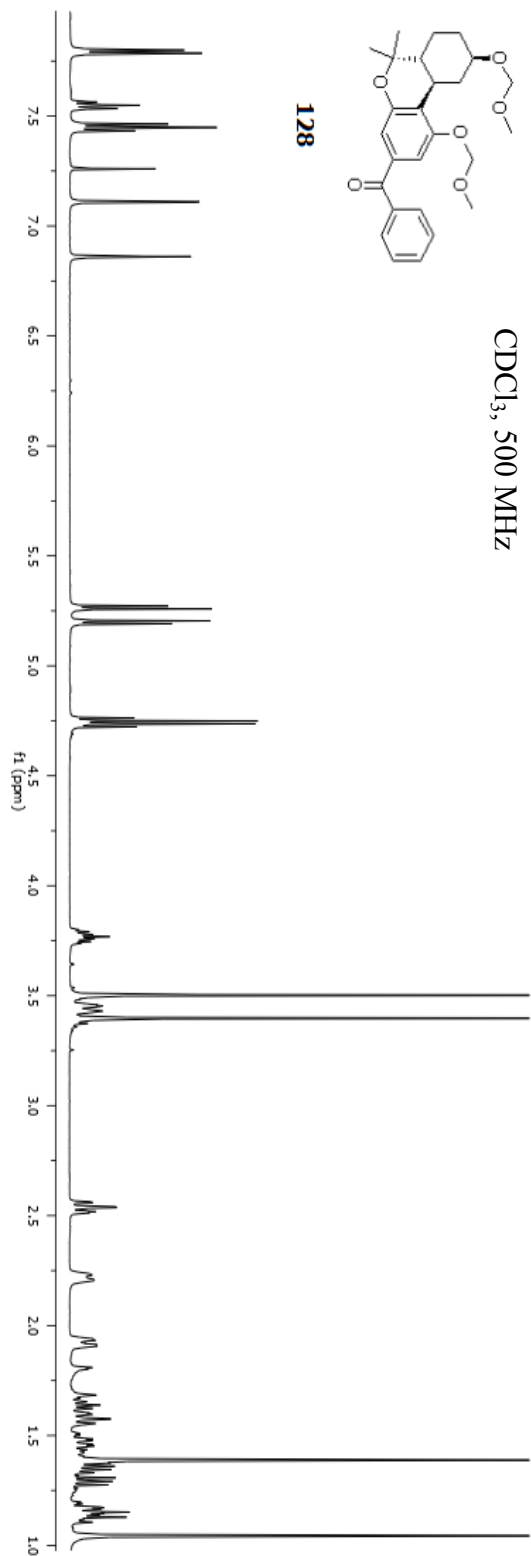
$[\alpha]_{\text{D}}^{23}$  -158 ( $c$  0.008, EtOAc)

## **APPENDIX 2: SPECTRA FOR SELECTED COMPOUNDS IN PART II**

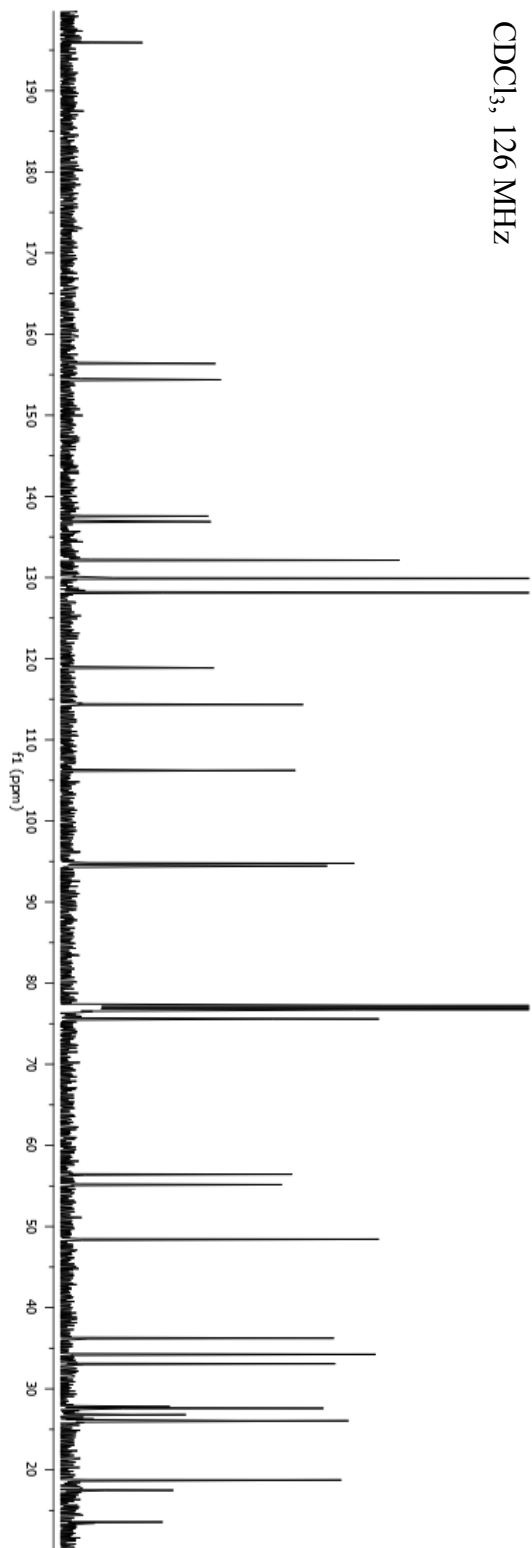
CDCl<sub>3</sub>, 500 MHz



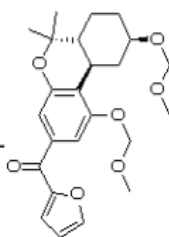
**128**



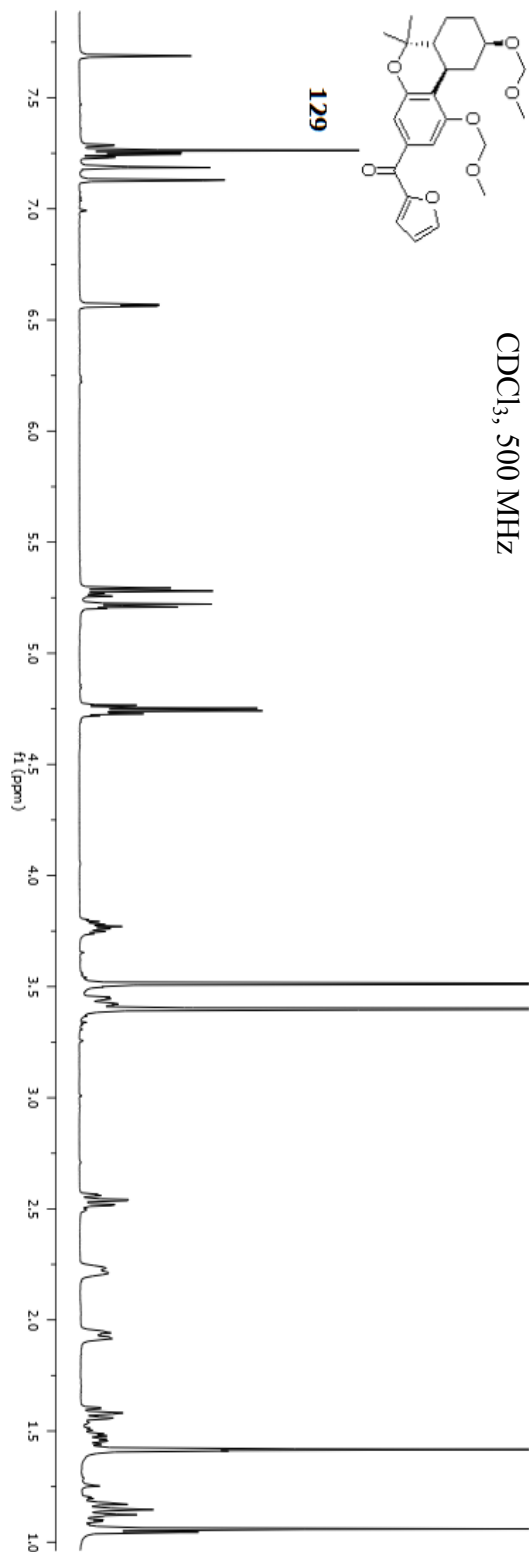
CDCl<sub>3</sub>, 126 MHz



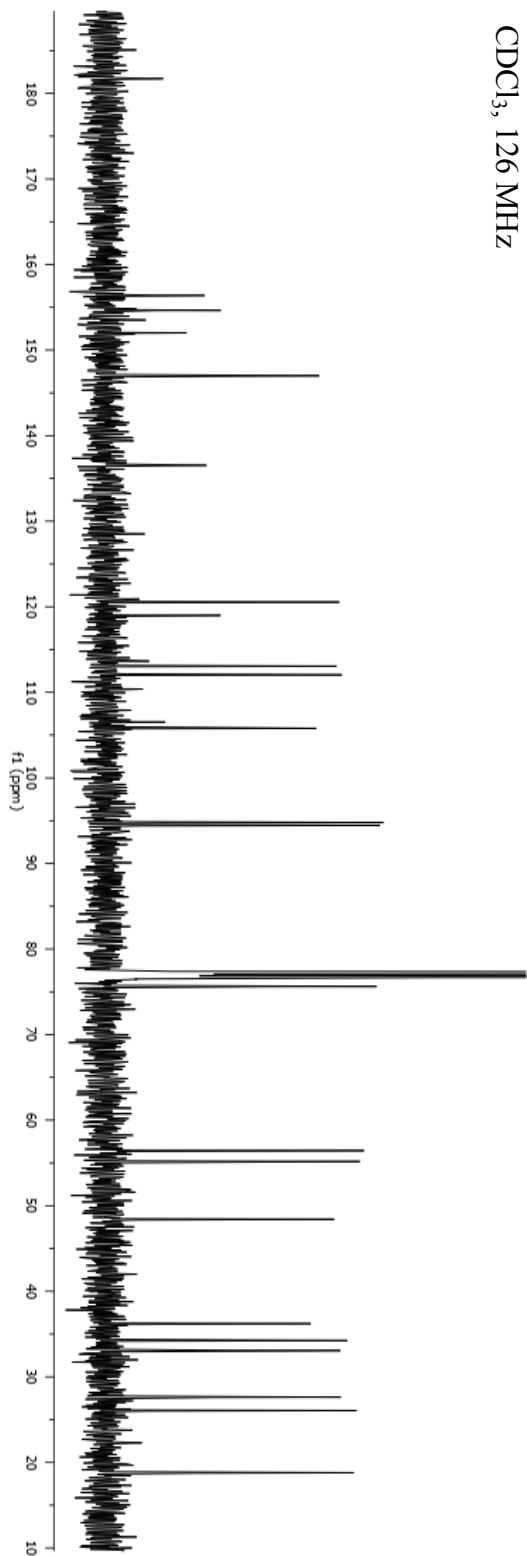
CDCl<sub>3</sub>, 500 MHz



**129**

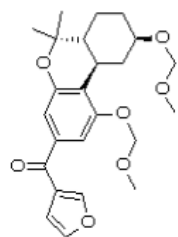


CDCl<sub>3</sub>, 126 MHz

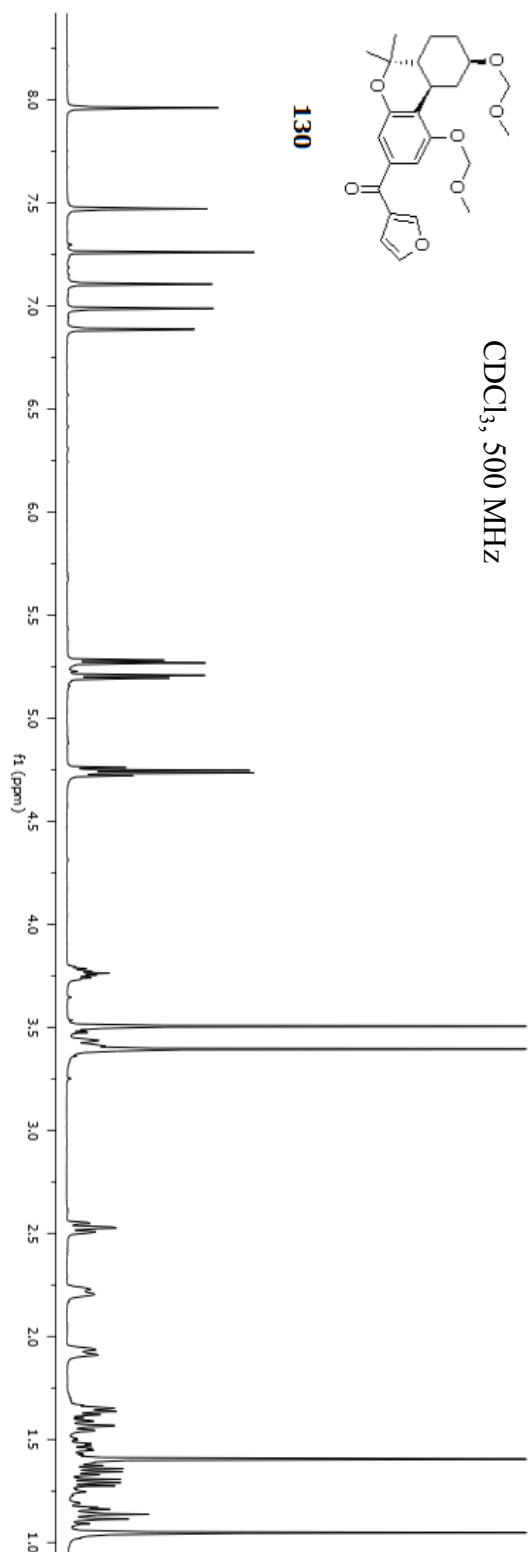




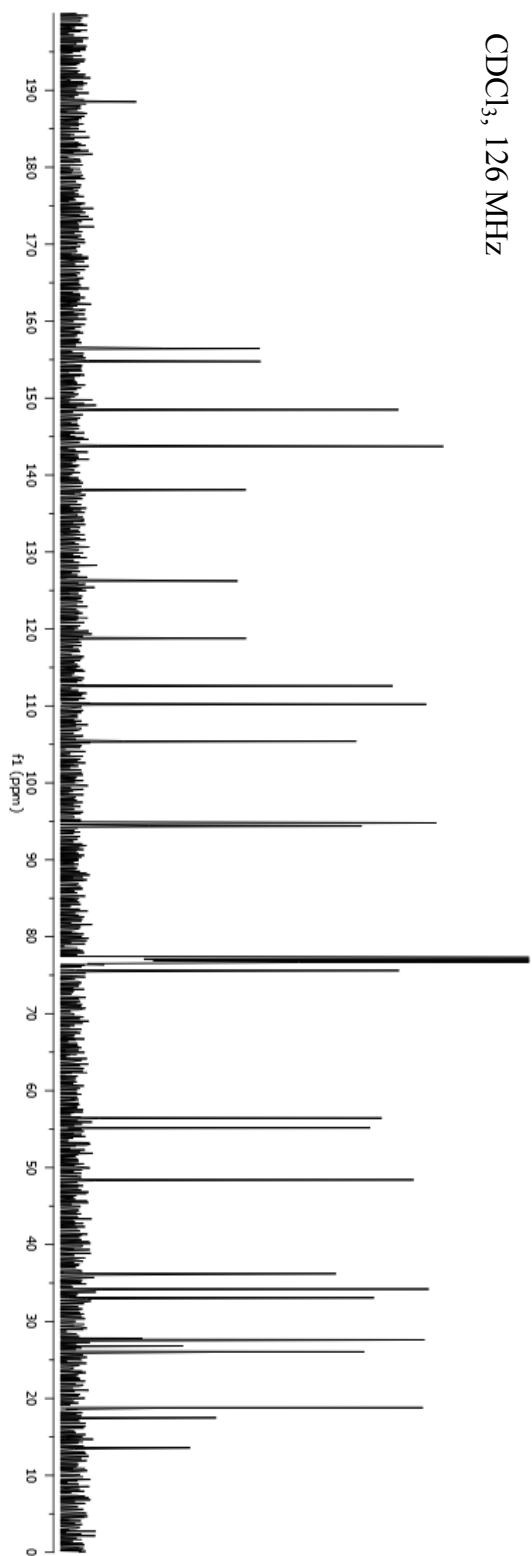
CDCl<sub>3</sub>, 500 MHz



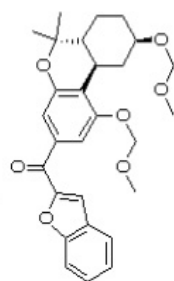
**130**



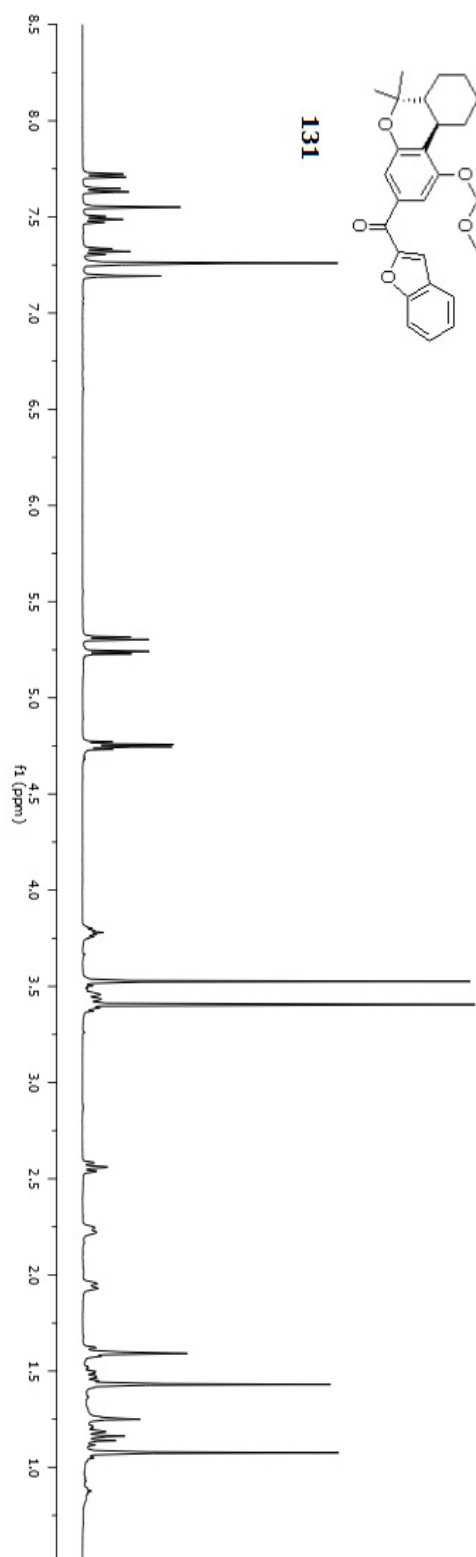
CDCl<sub>3</sub>, 126 MHz



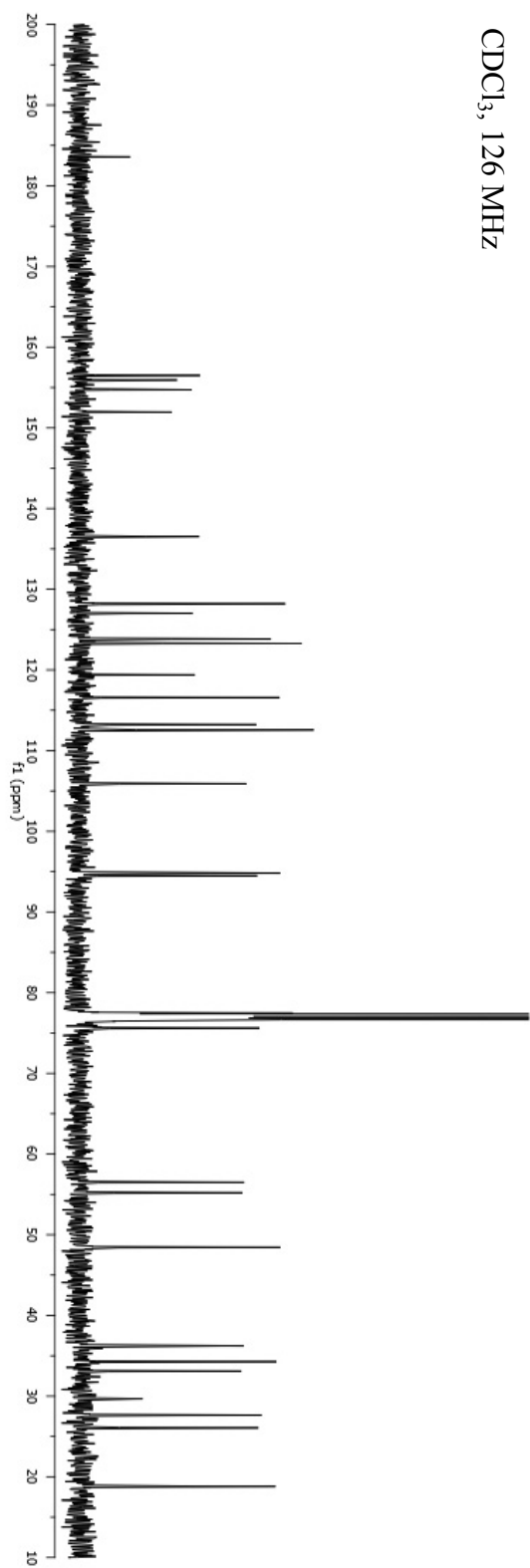
CDCl<sub>3</sub>, 500 MHz



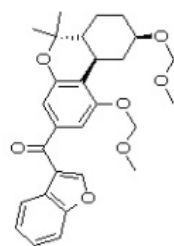
**131**



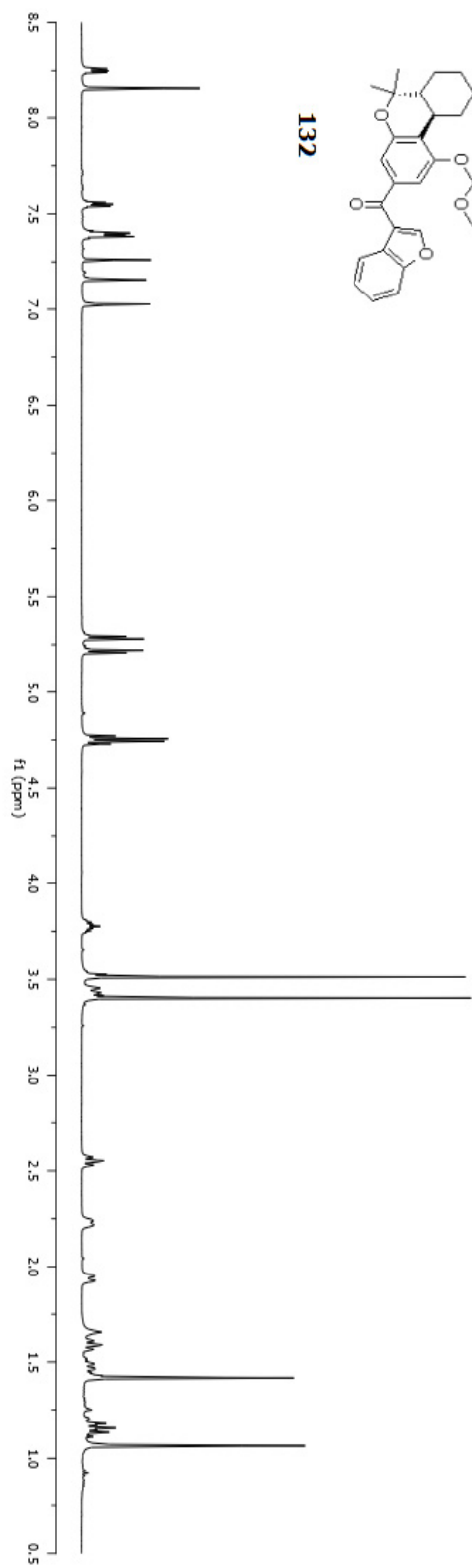
CDCl<sub>3</sub>, 126 MHz



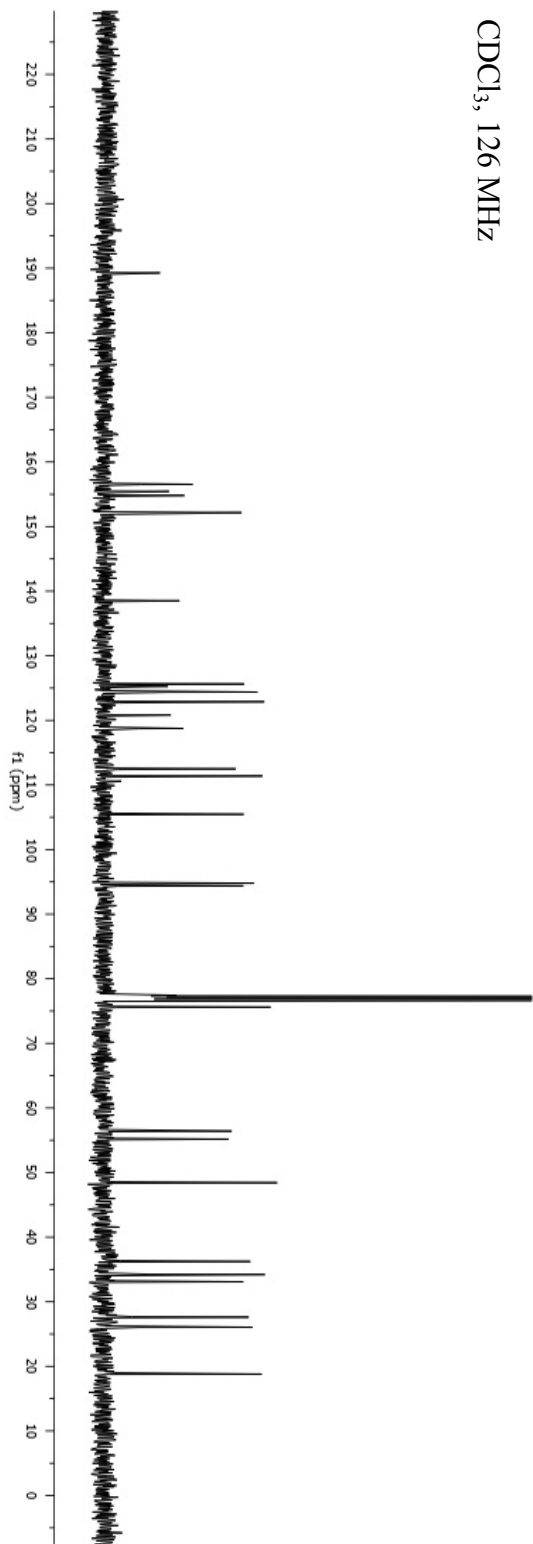
CDCl<sub>3</sub>, 500 MHz

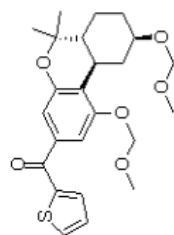


**132**



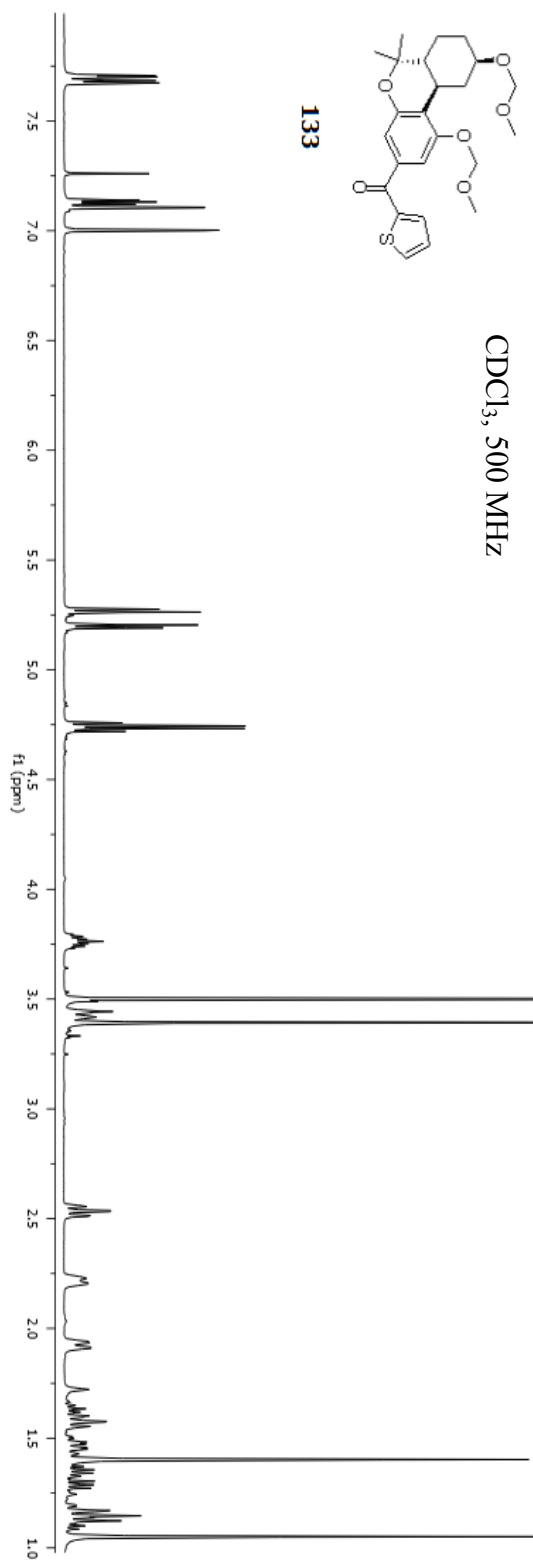
CDCl<sub>3</sub>, 126 MHz



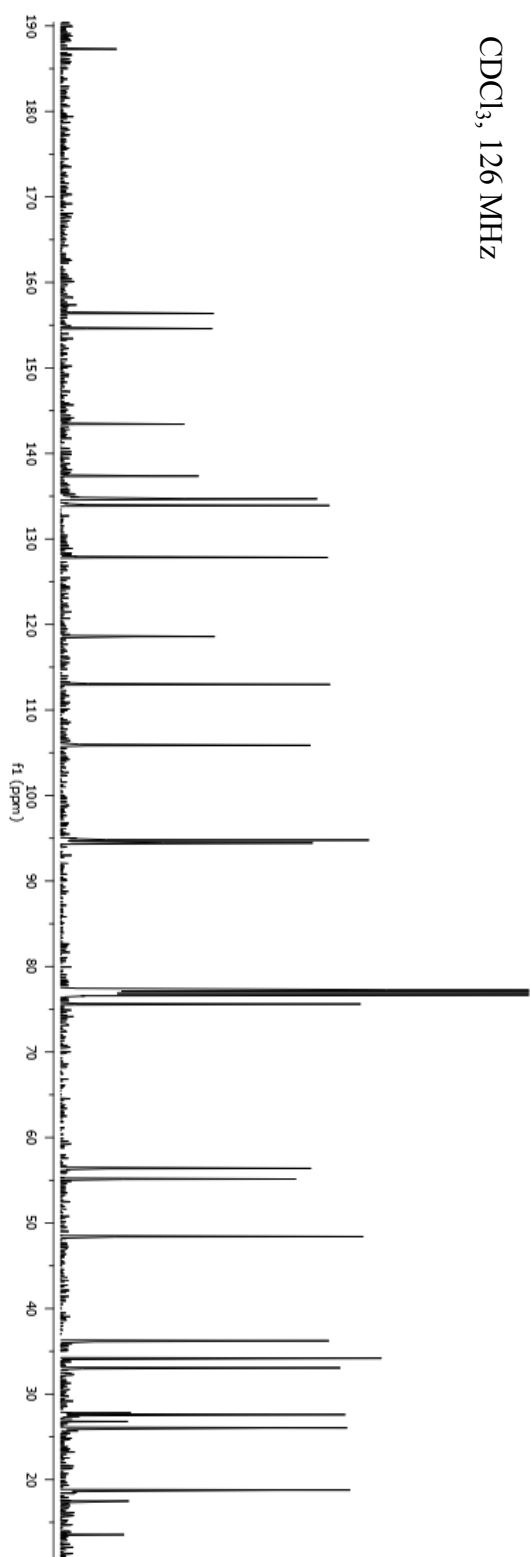


**133**

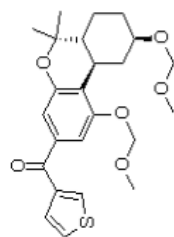
CDCl<sub>3</sub>, 500 MHz



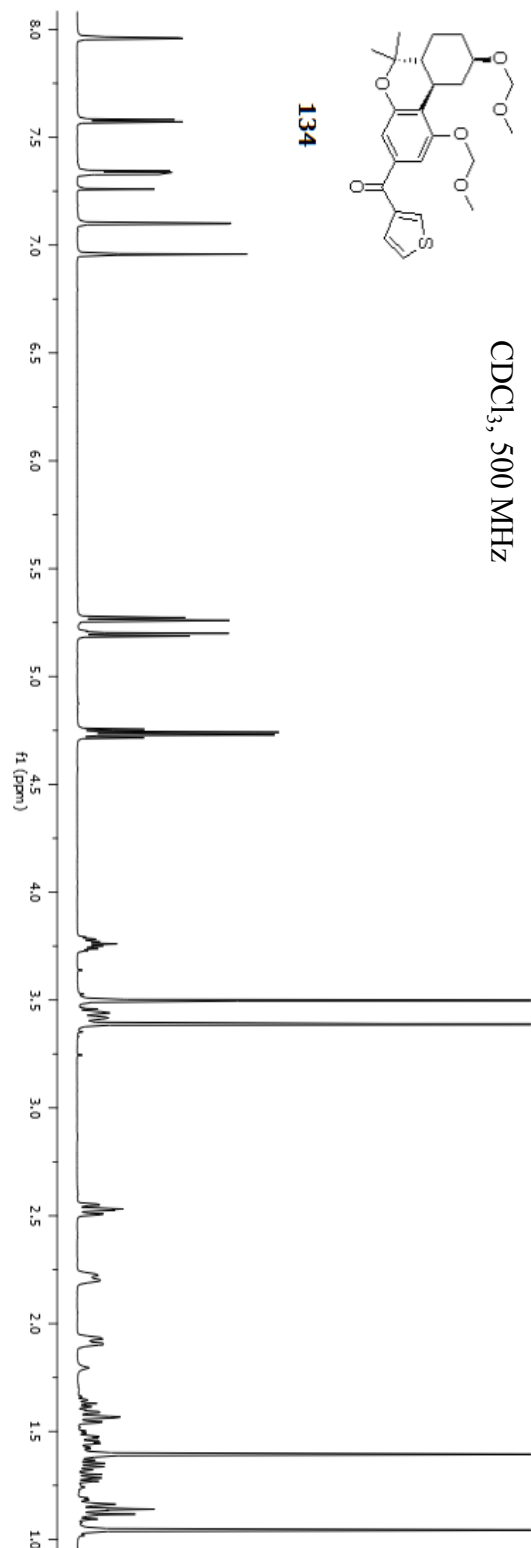
CDCl<sub>3</sub>, 126 MHz



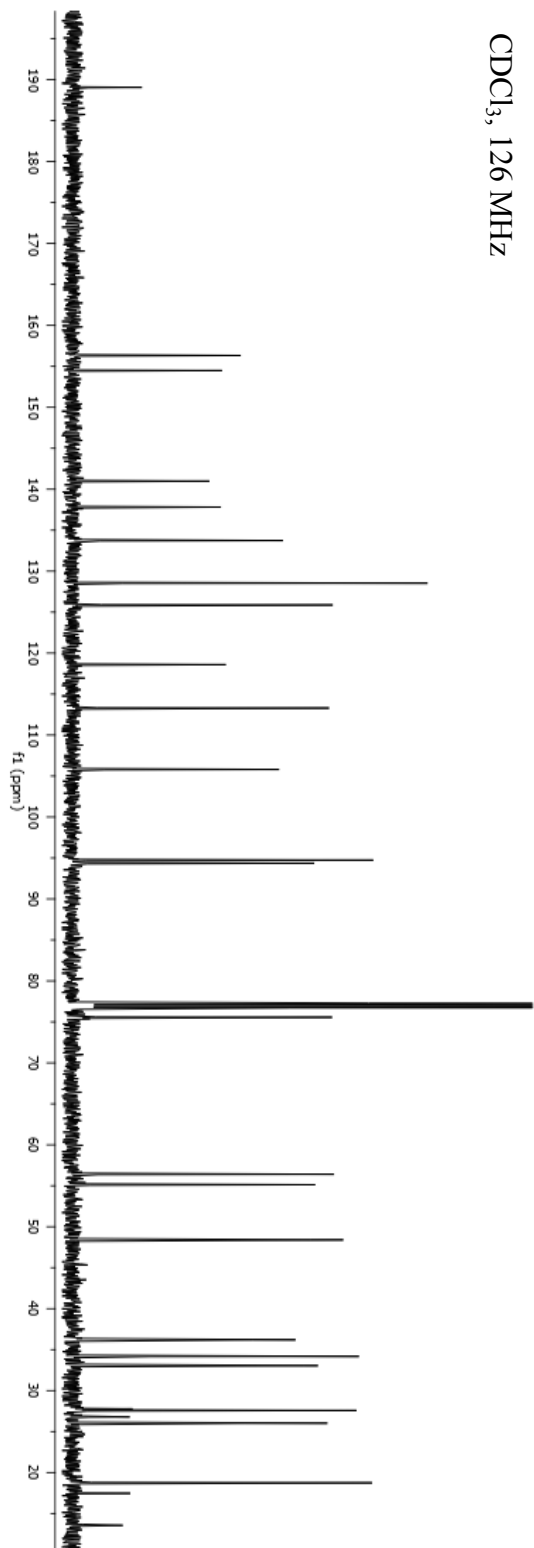
CDCl<sub>3</sub>, 500 MHz

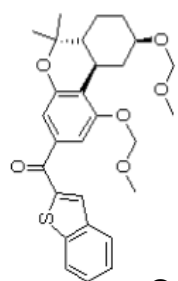


**134**



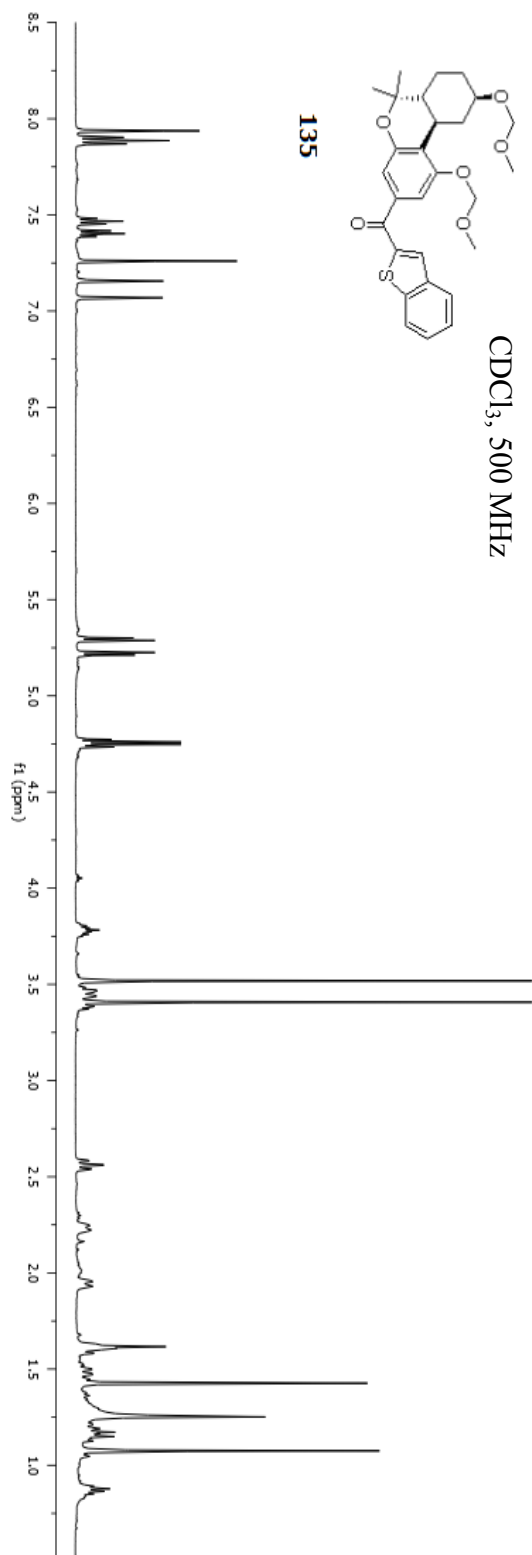
CDCl<sub>3</sub>, 126 MHz



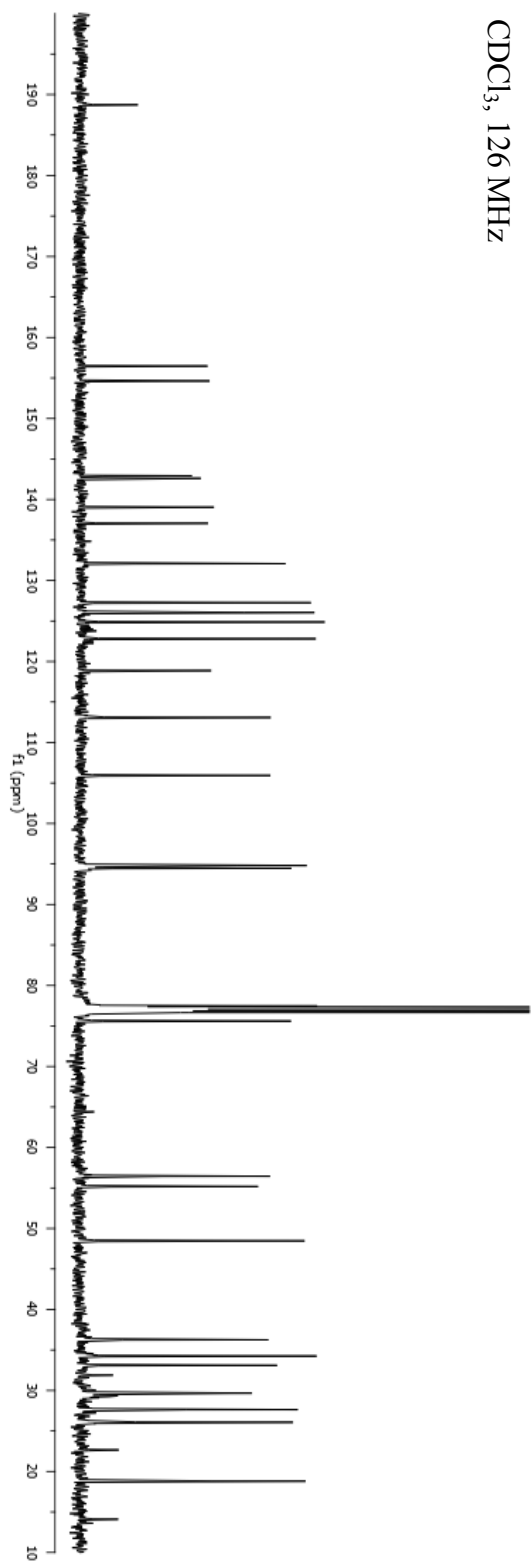


CDCl<sub>3</sub>, 500 MHz

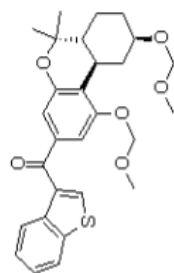
**135**



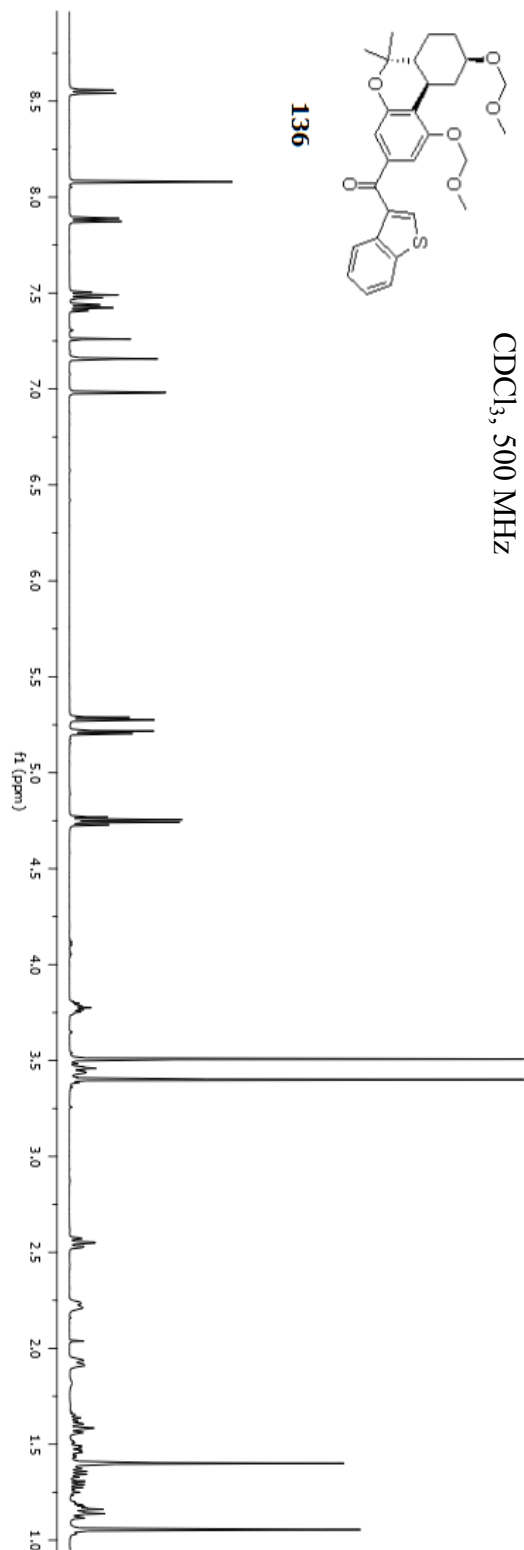
CDCl<sub>3</sub>, 126 MHz



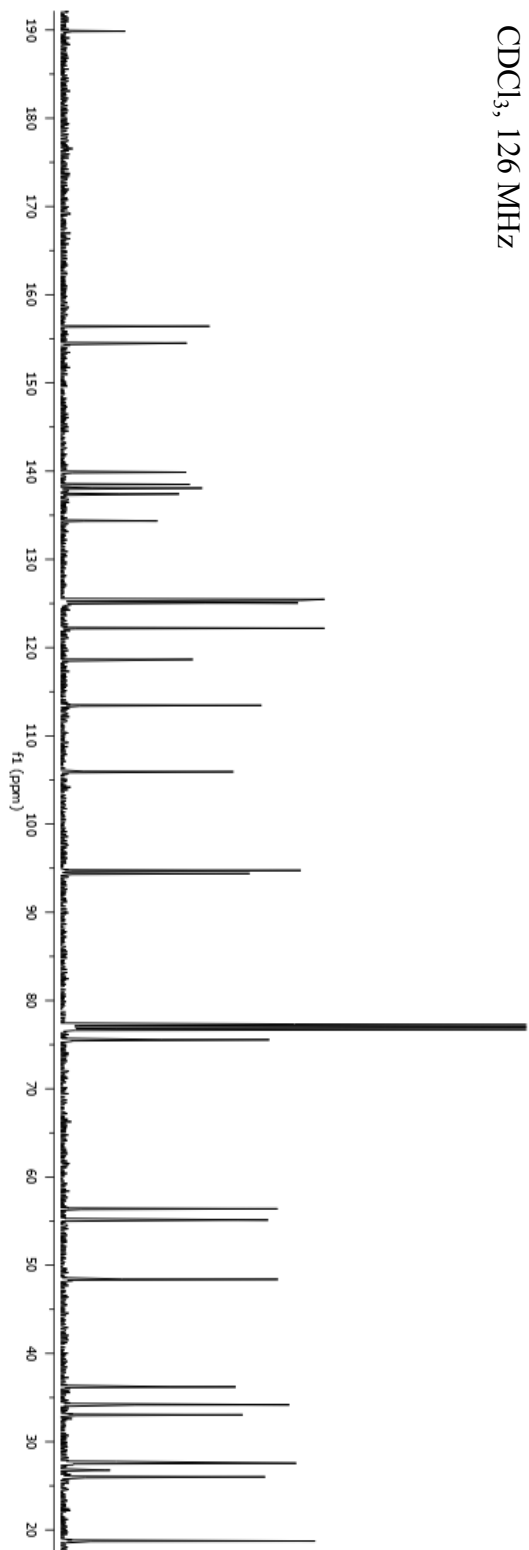
CDCl<sub>3</sub>, 500 MHz

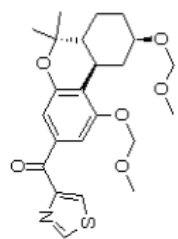


**136**



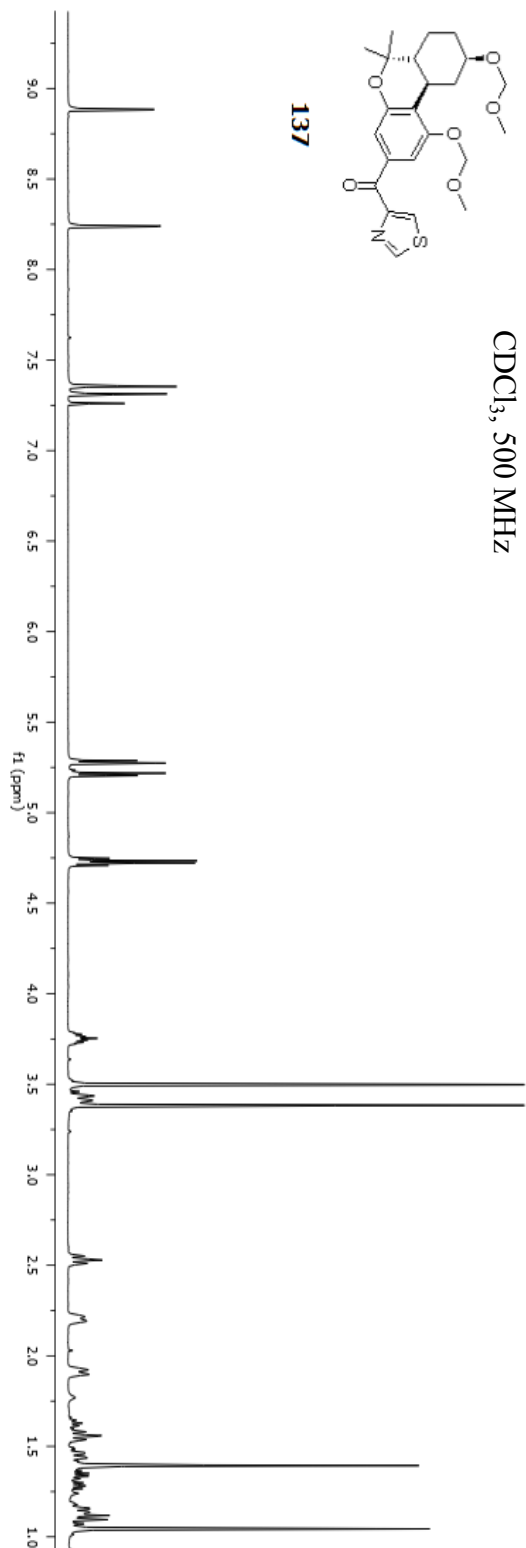
CDCl<sub>3</sub>, 126 MHz



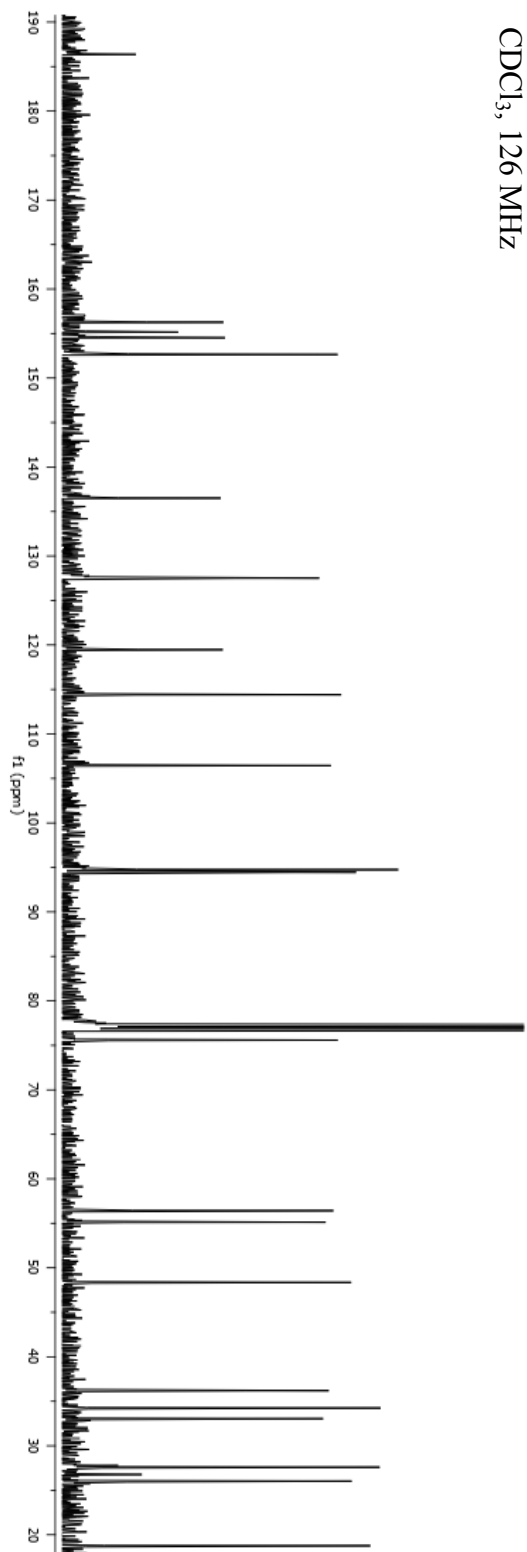


**137**

CDCl<sub>3</sub>, 500 MHz

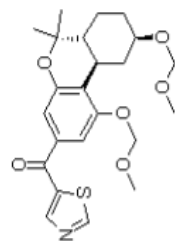


CDCl<sub>3</sub>, 126 MHz

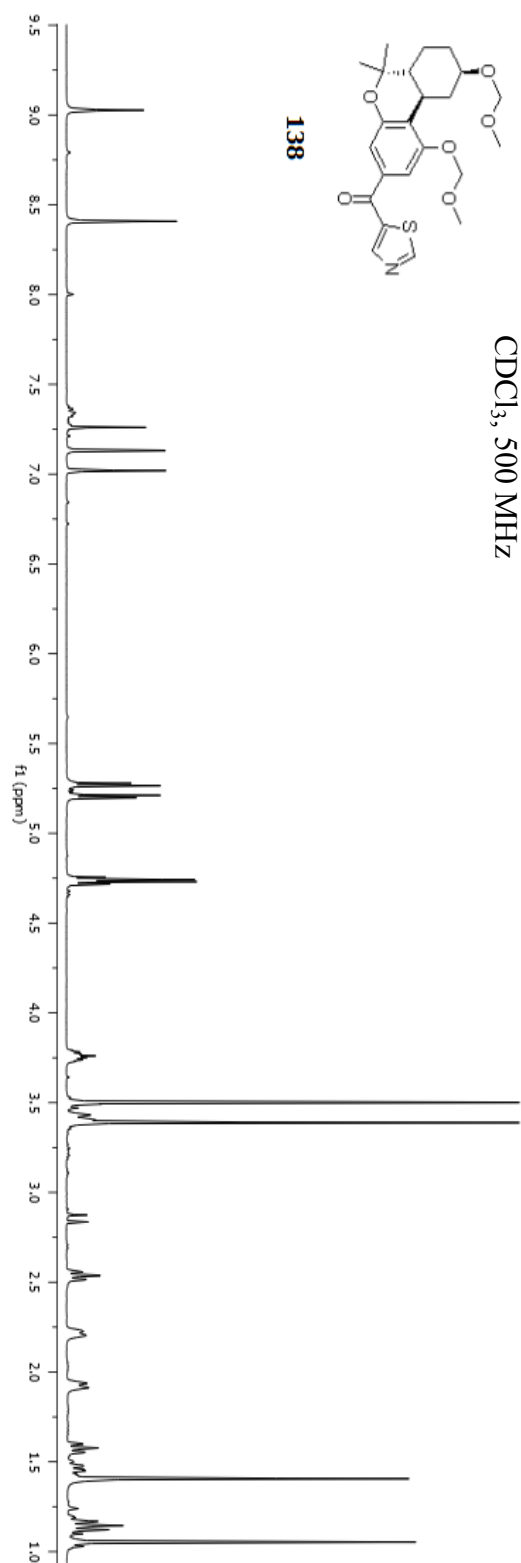




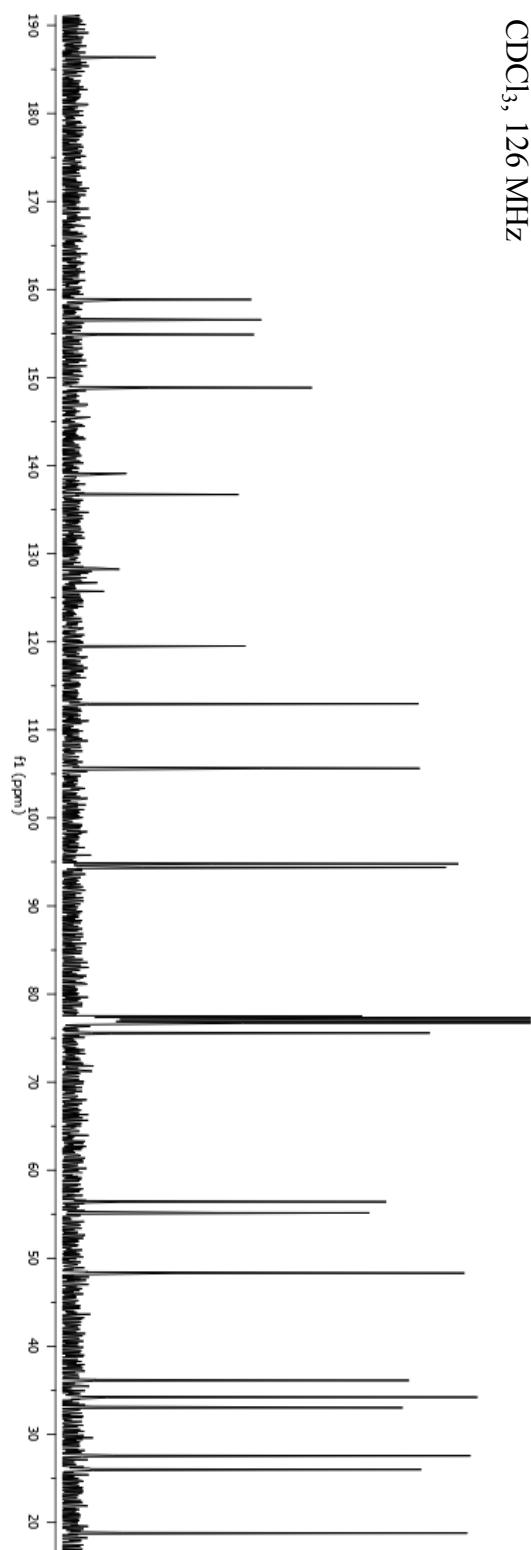
CDCl<sub>3</sub>, 500 MHz



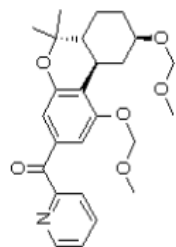
**138**



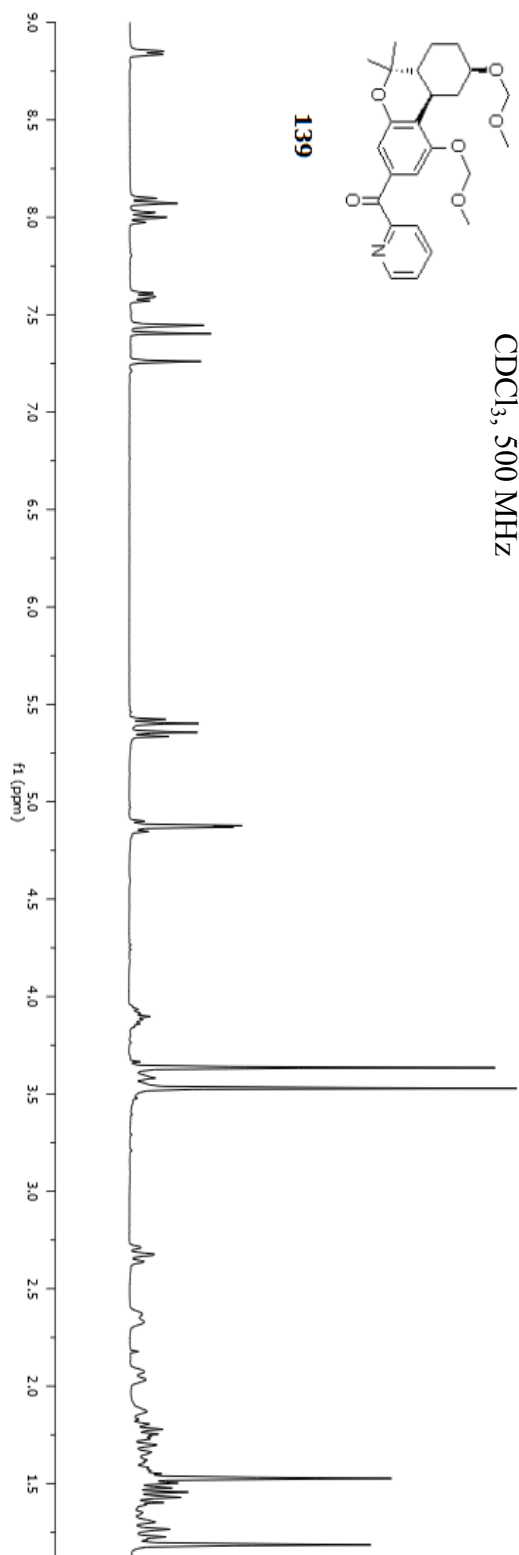
CDCl<sub>3</sub>, 126 MHz



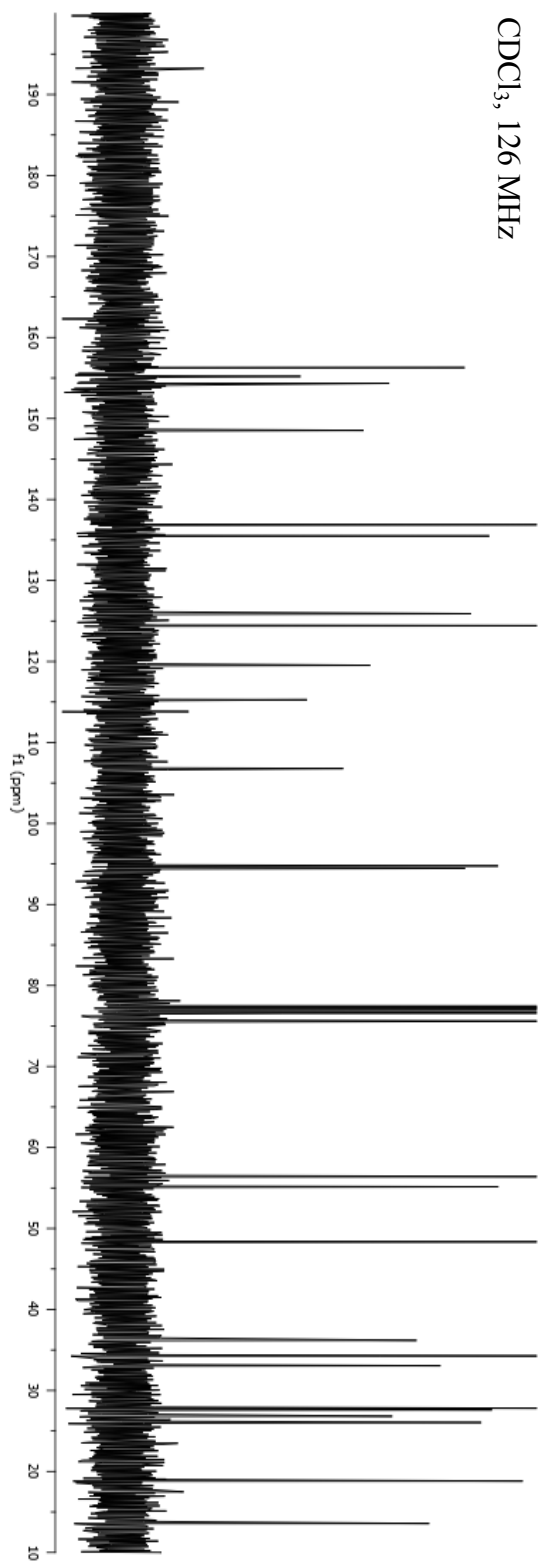
CDCl<sub>3</sub>, 500 MHz



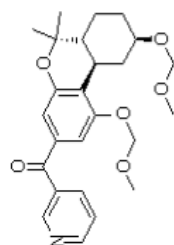
**139**



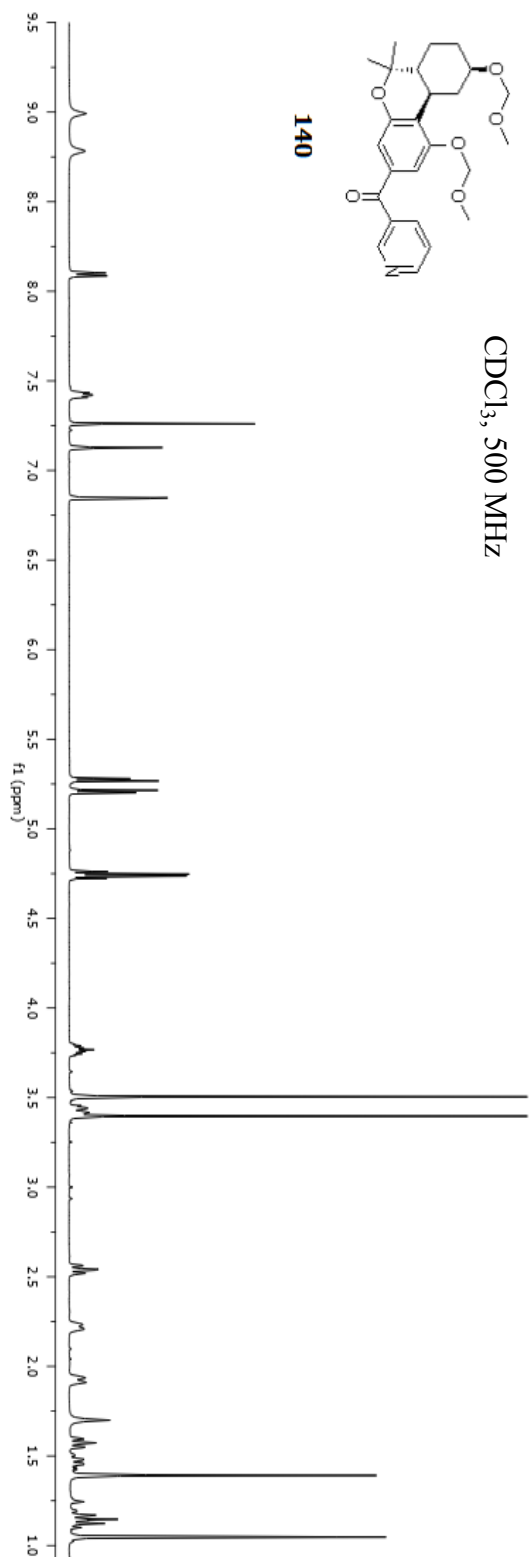
CDCl<sub>3</sub>, 126 MHz



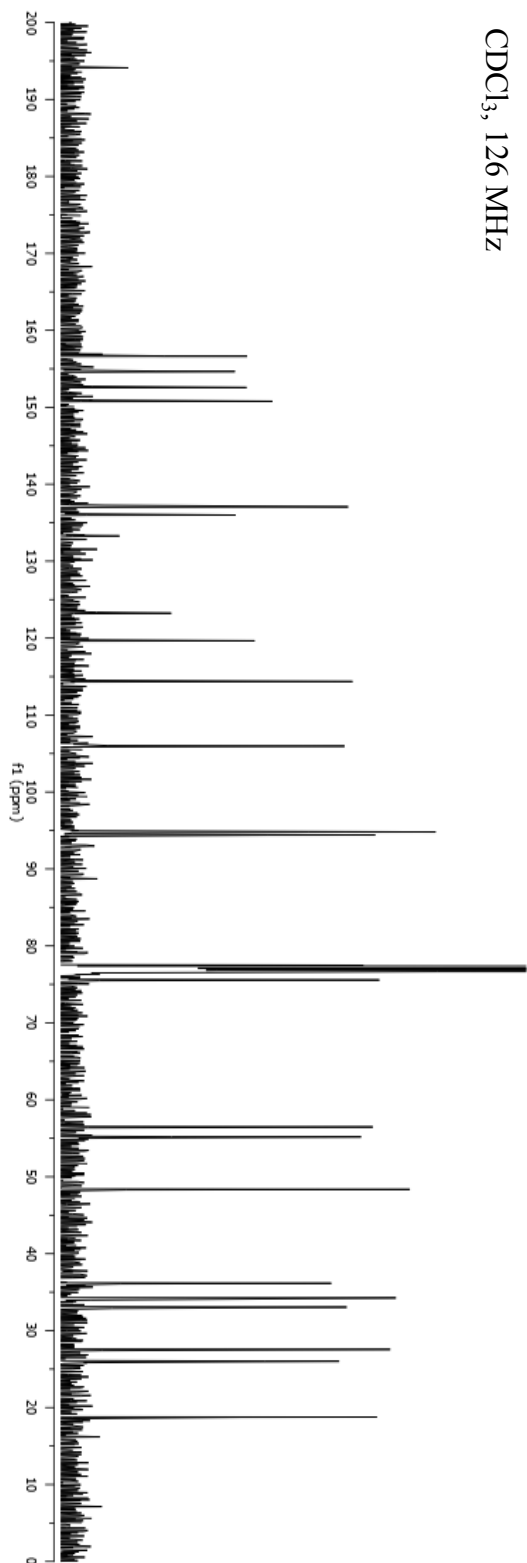
CDCl<sub>3</sub>, 500 MHz



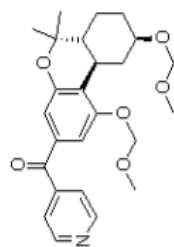
**140**



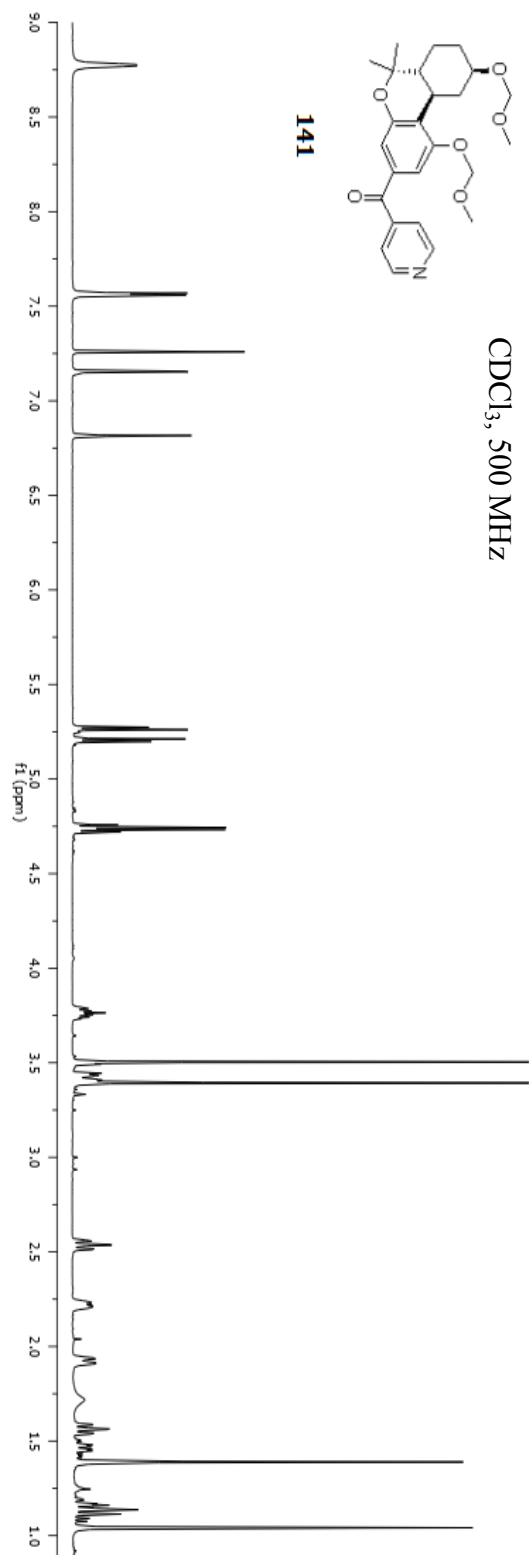
CDCl<sub>3</sub>, 126 MHz



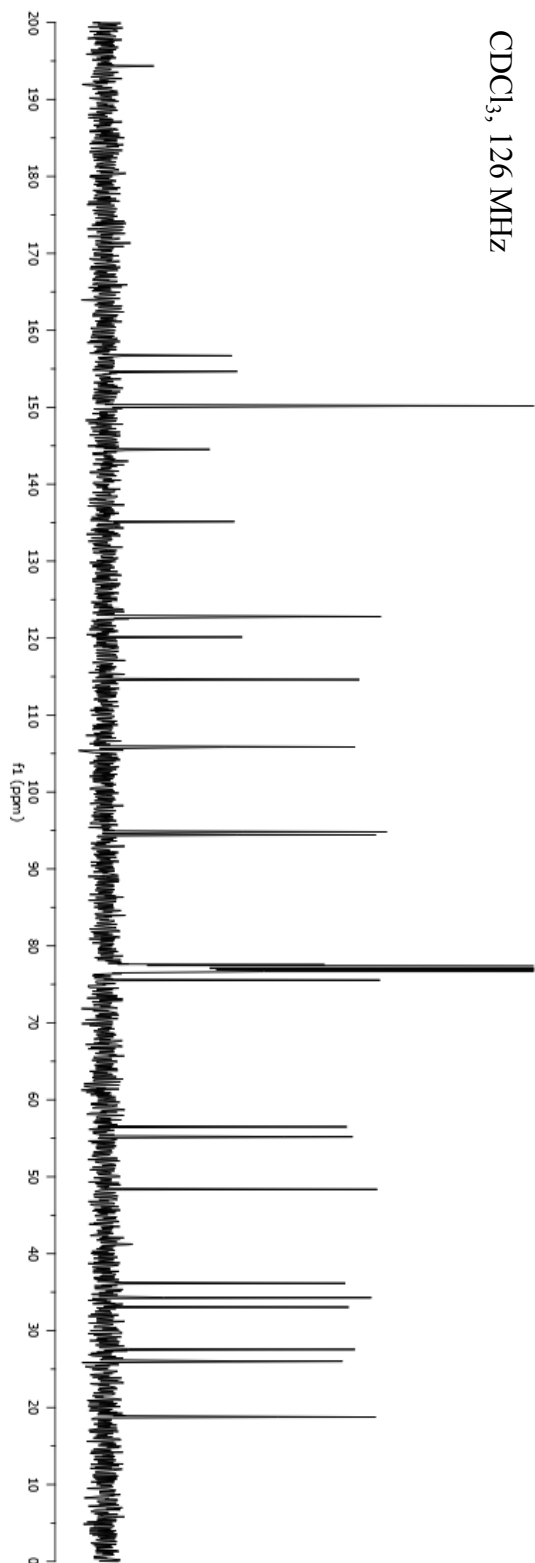
CDCl<sub>3</sub>, 500 MHz

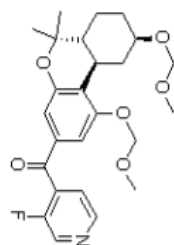


**141**



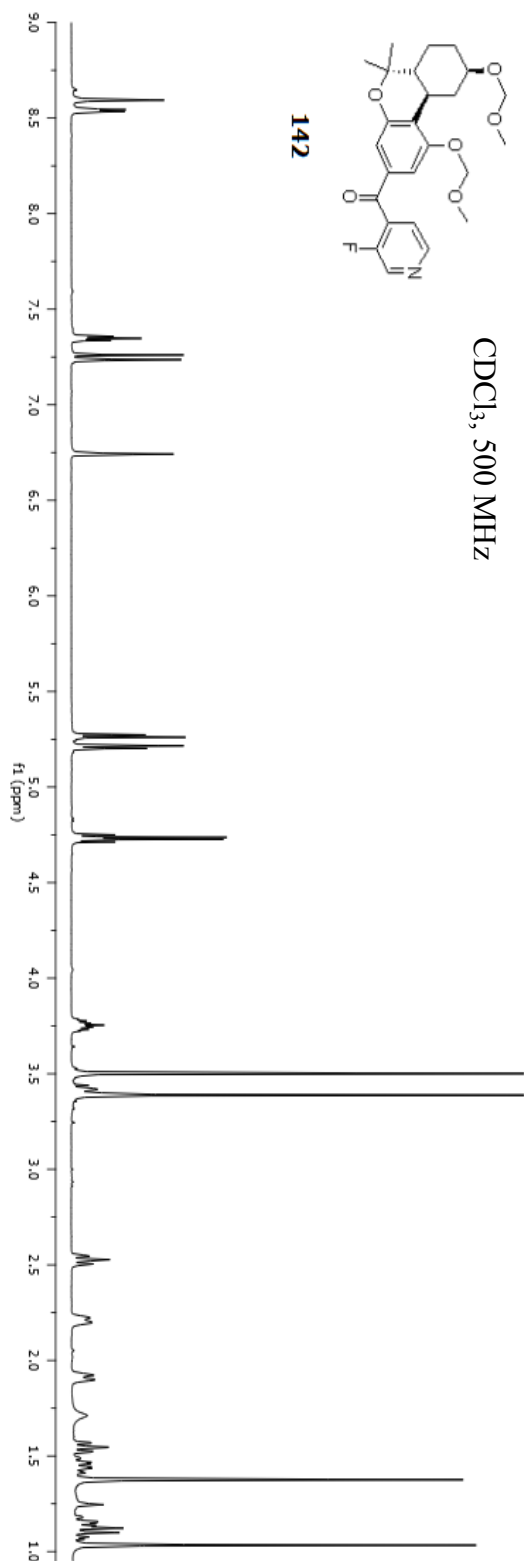
CDCl<sub>3</sub>, 126 MHz



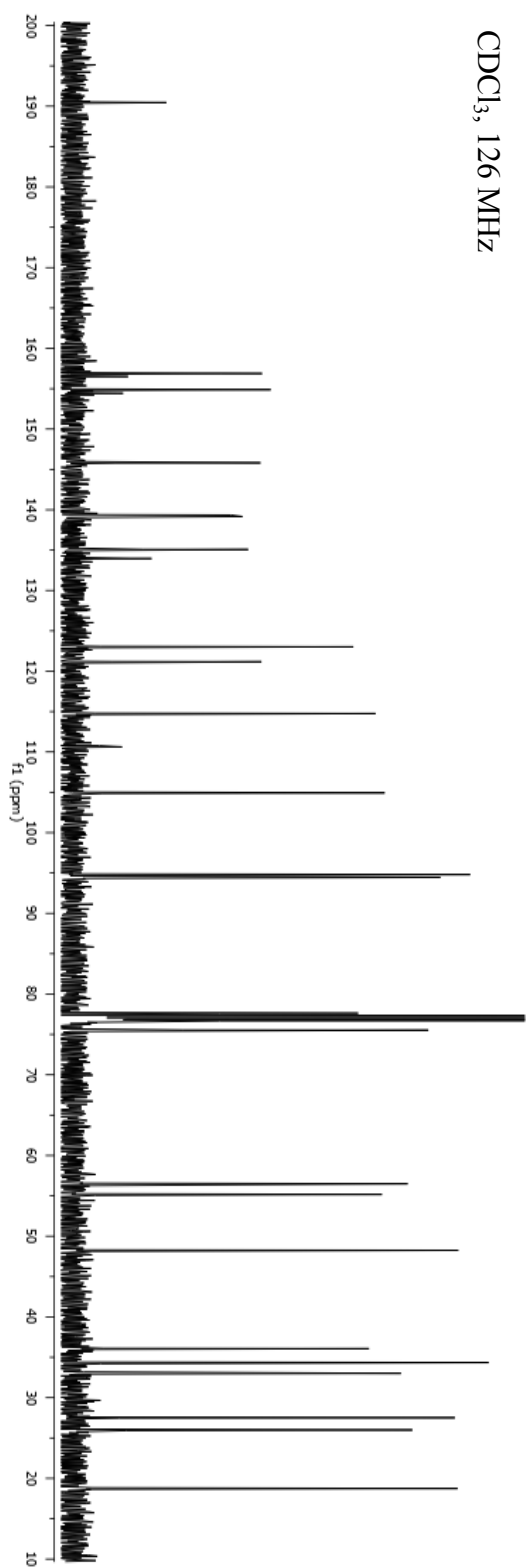


**142**

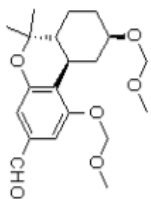
CDCl<sub>3</sub>, 500 MHz



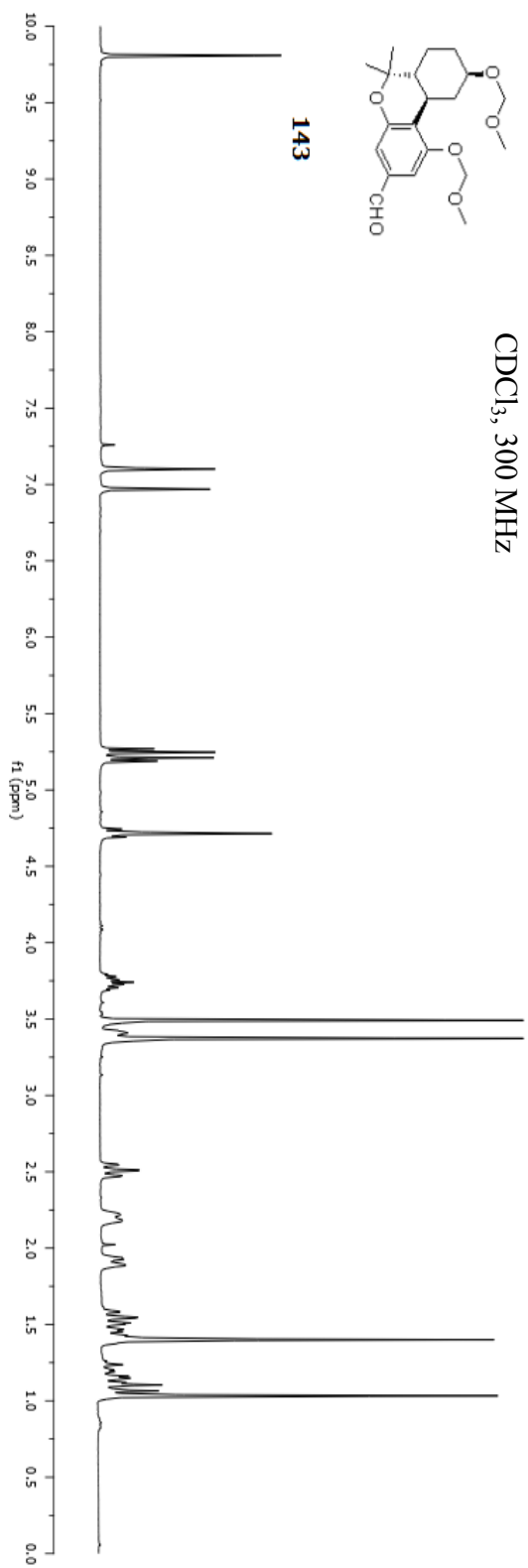
CDCl<sub>3</sub>, 126 MHz



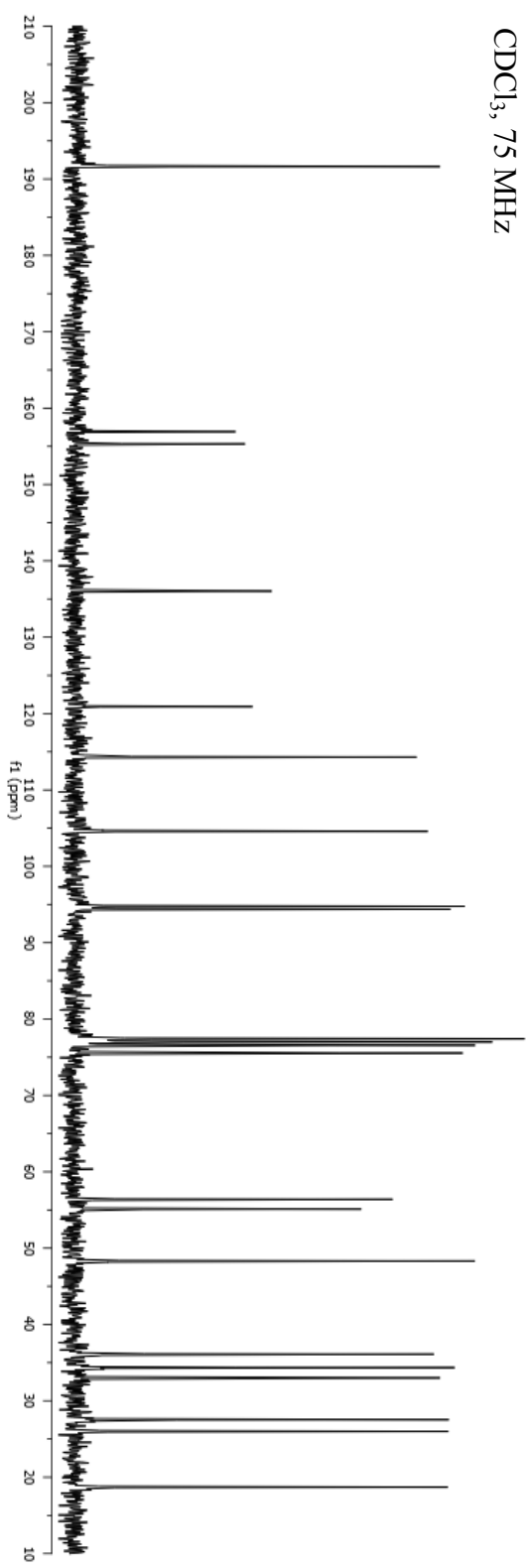
CDCl<sub>3</sub>, 300 MHz



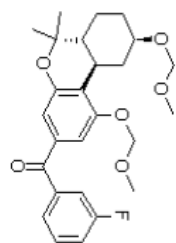
**143**



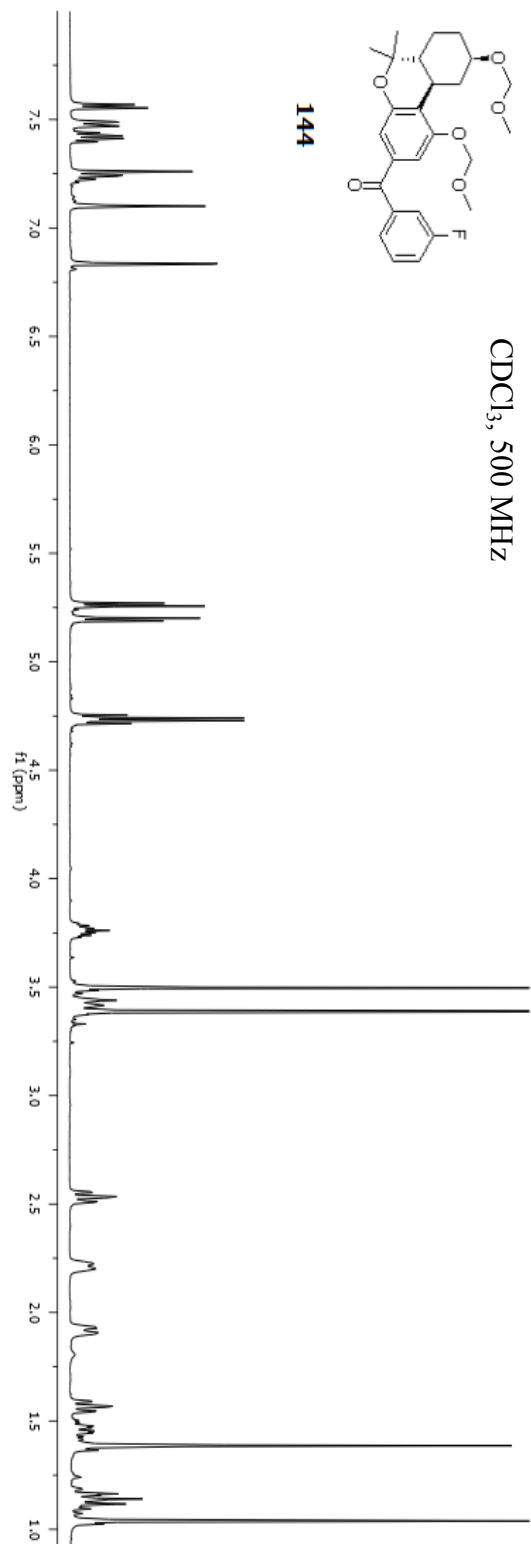
CDCl<sub>3</sub>, 75 MHz



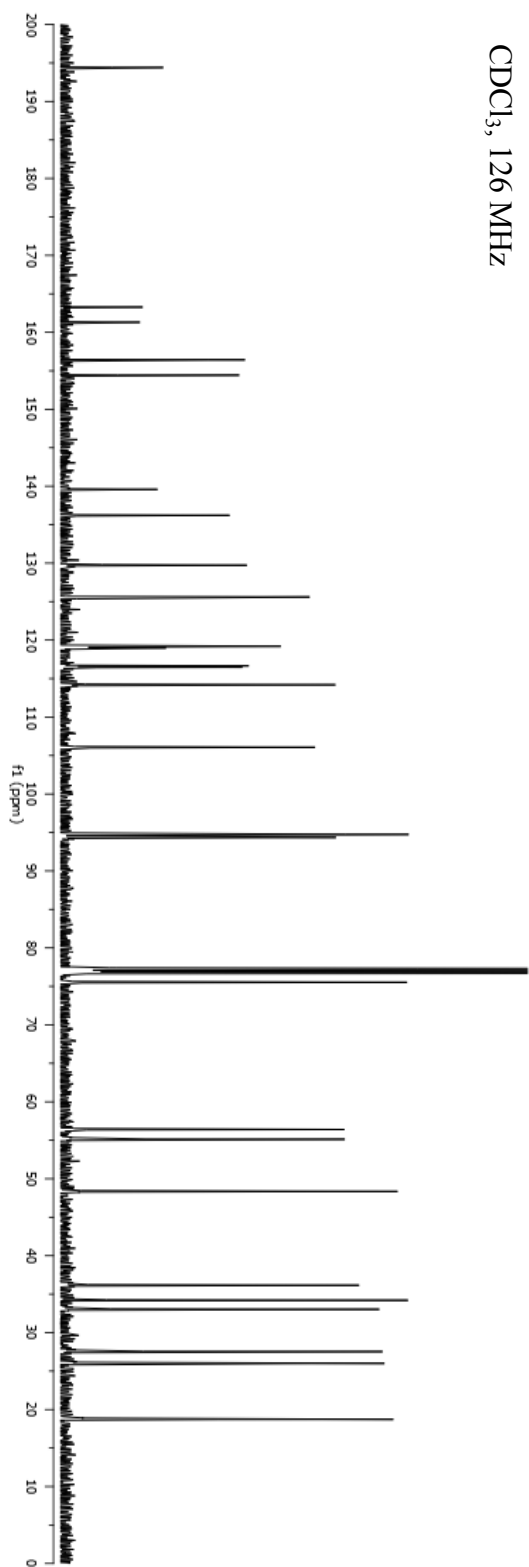
CDCl<sub>3</sub>, 500 MHz



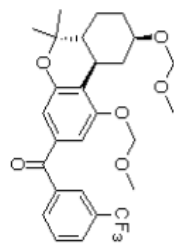
**144**



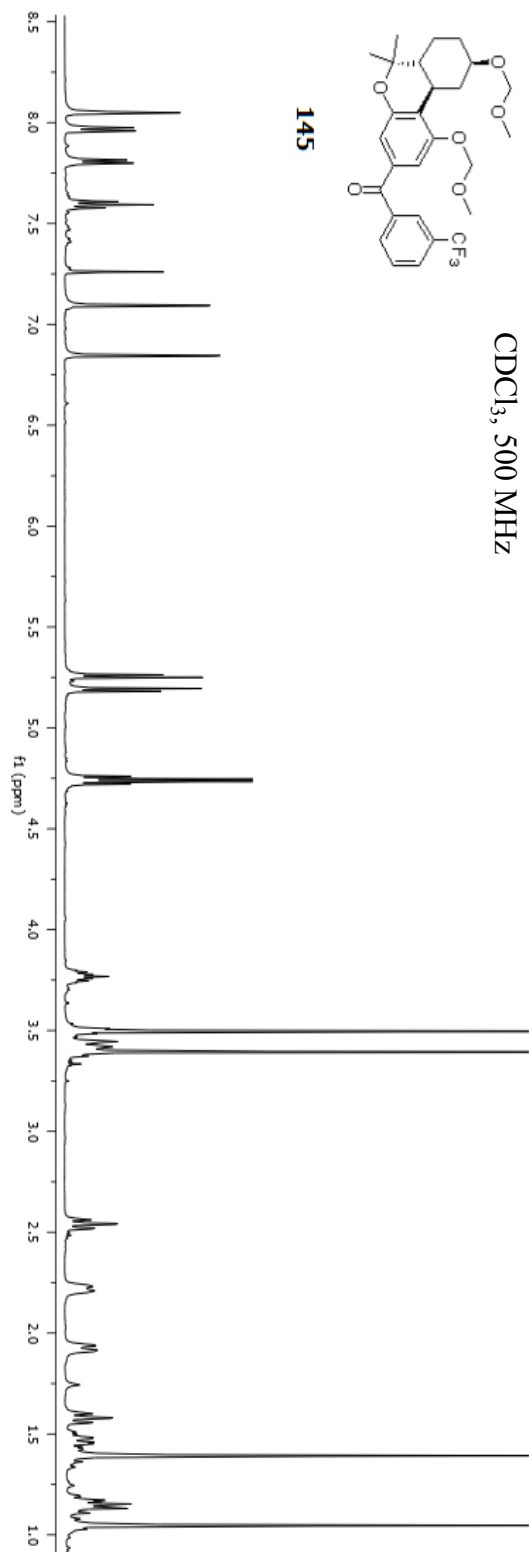
CDCl<sub>3</sub>, 126 MHz



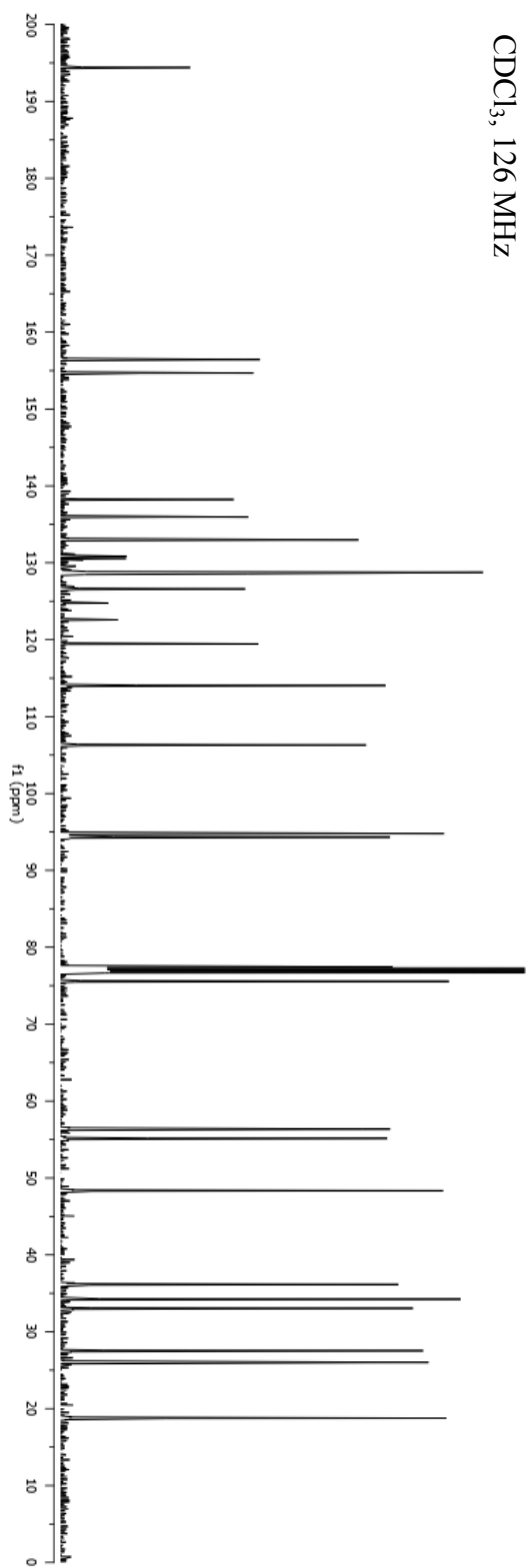
CDCl<sub>3</sub>, 500 MHz



**145**

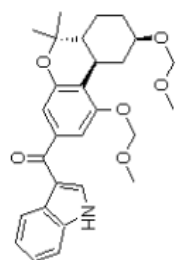


CDCl<sub>3</sub>, 126 MHz

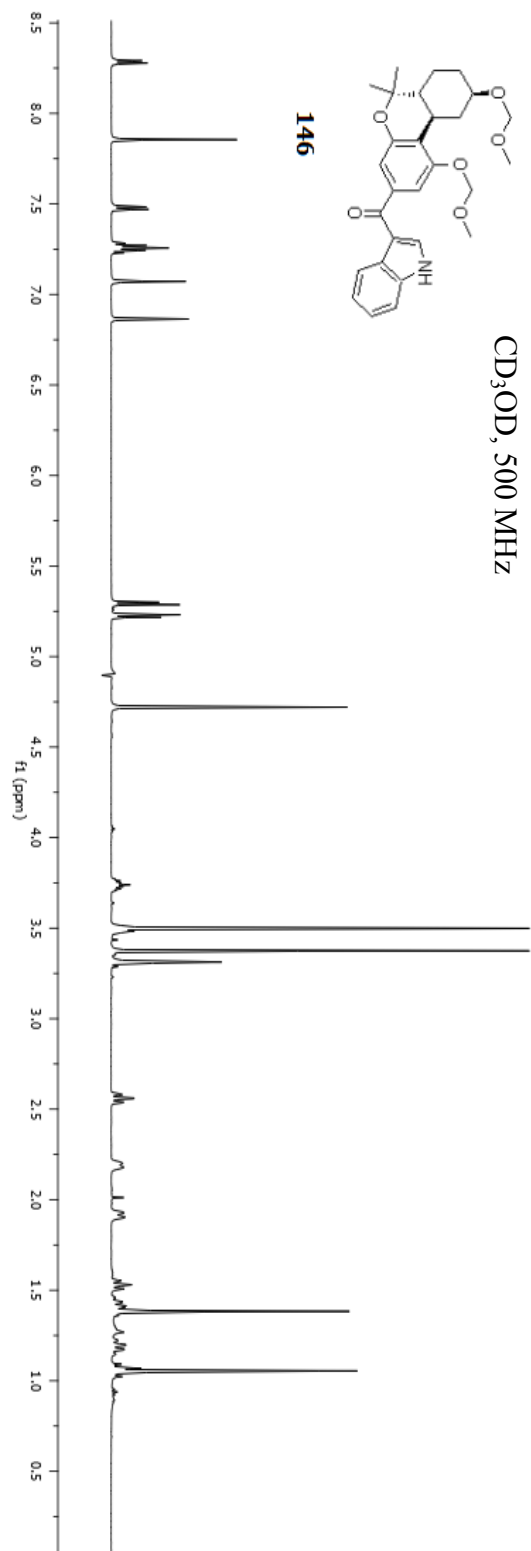




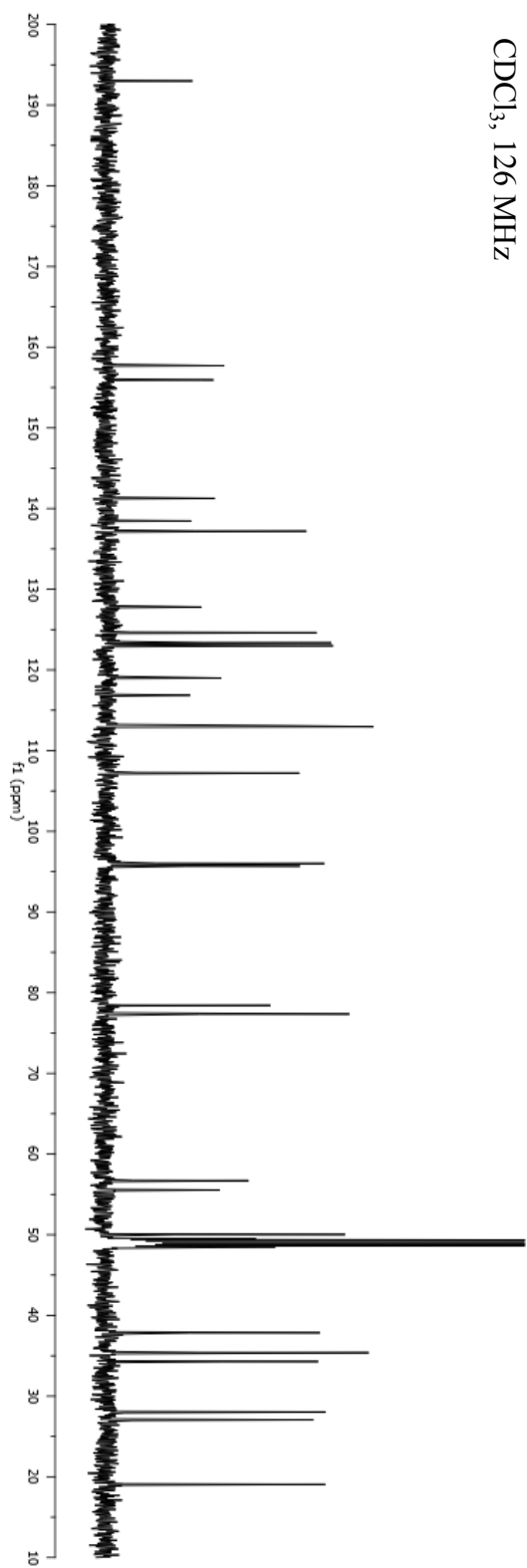
CD<sub>3</sub>OD, 500 MHz



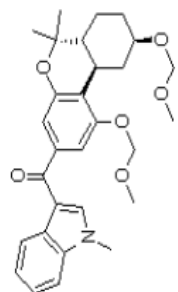
**146**



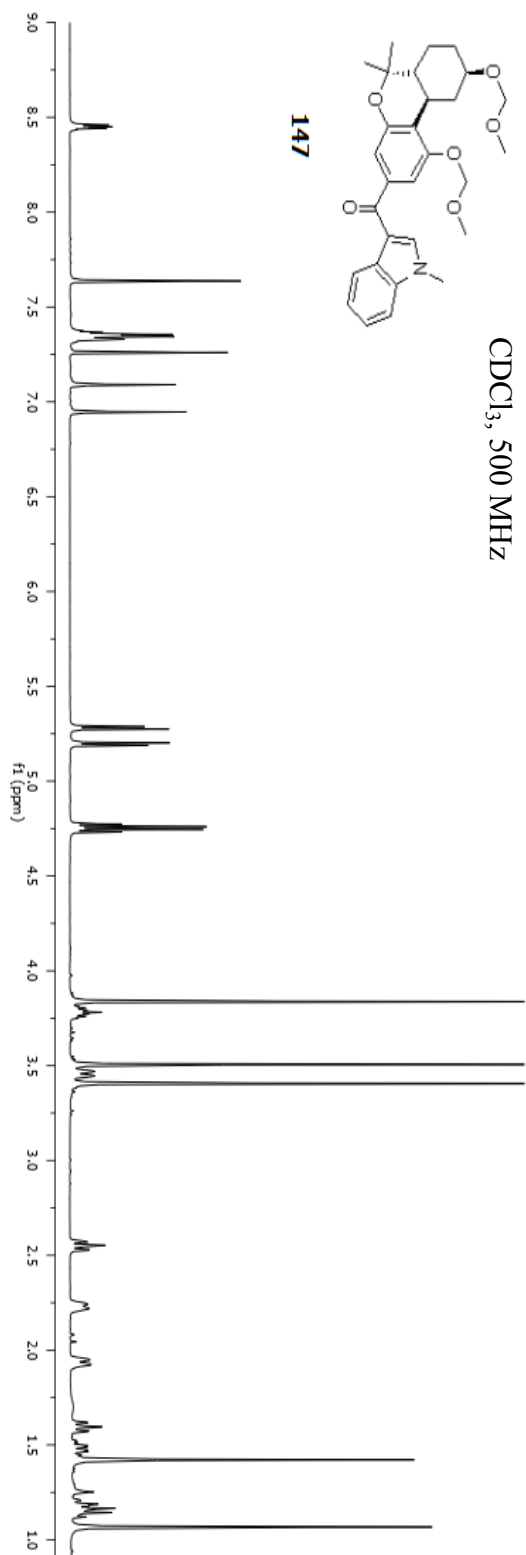
CDCl<sub>3</sub>, 126 MHz



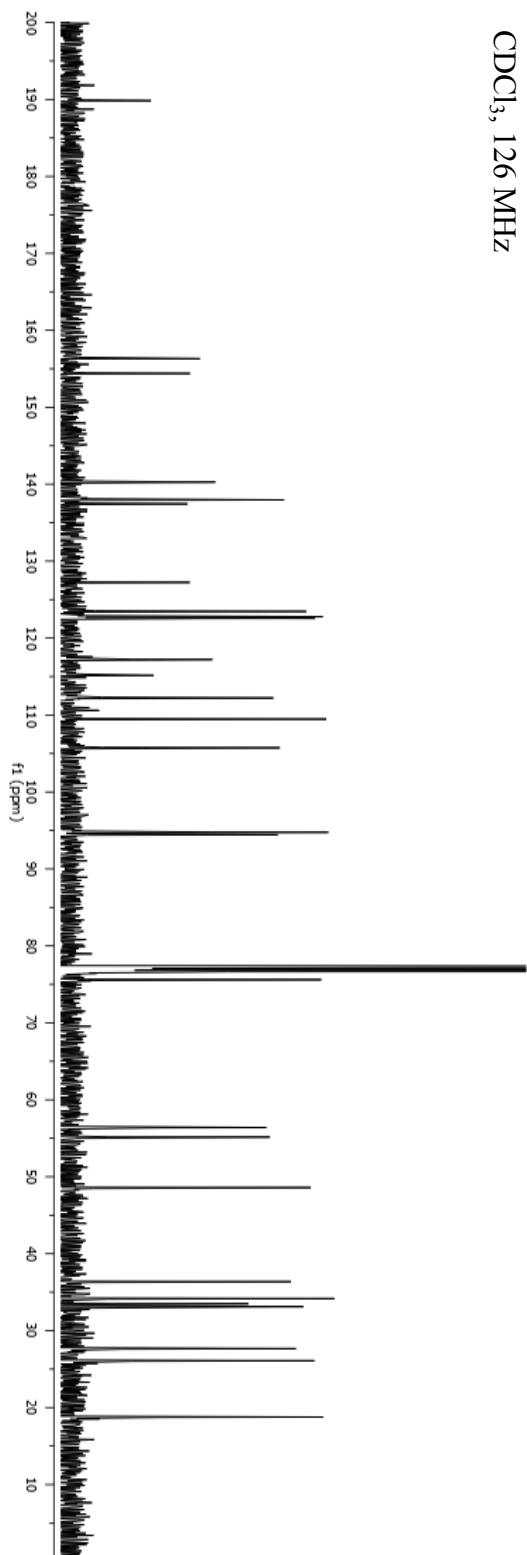
CDCl<sub>3</sub>, 500 MHz



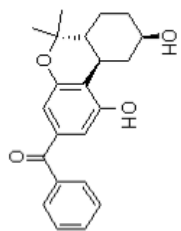
**147**



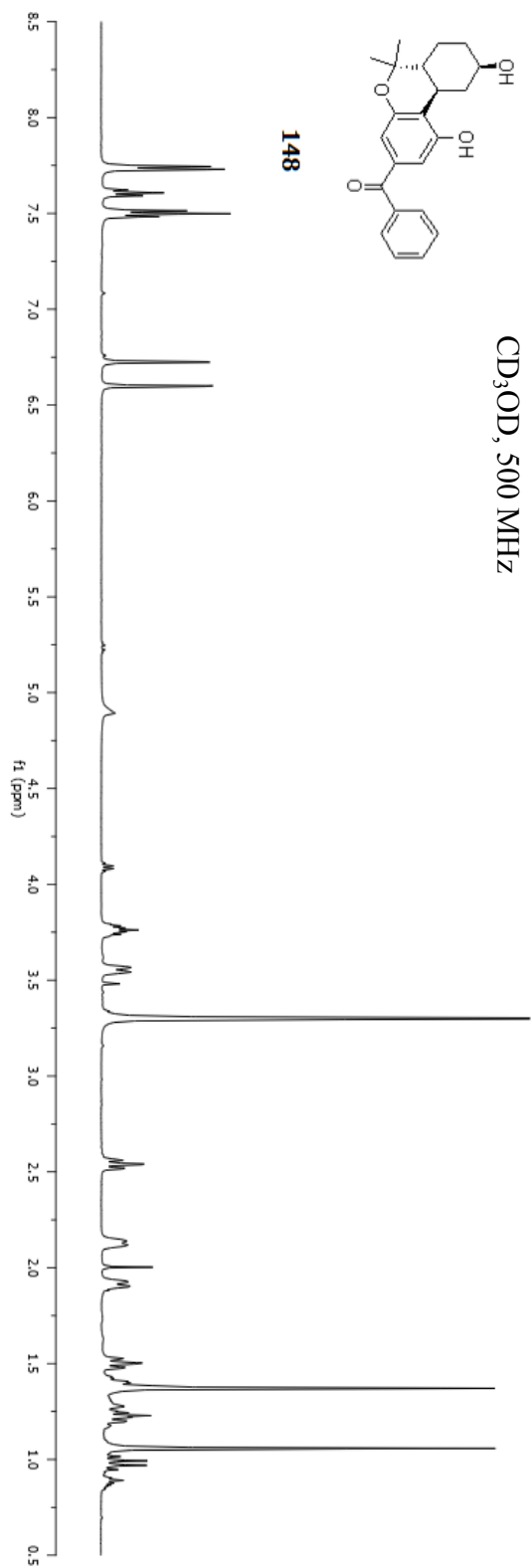
CDCl<sub>3</sub>, 126 MHz



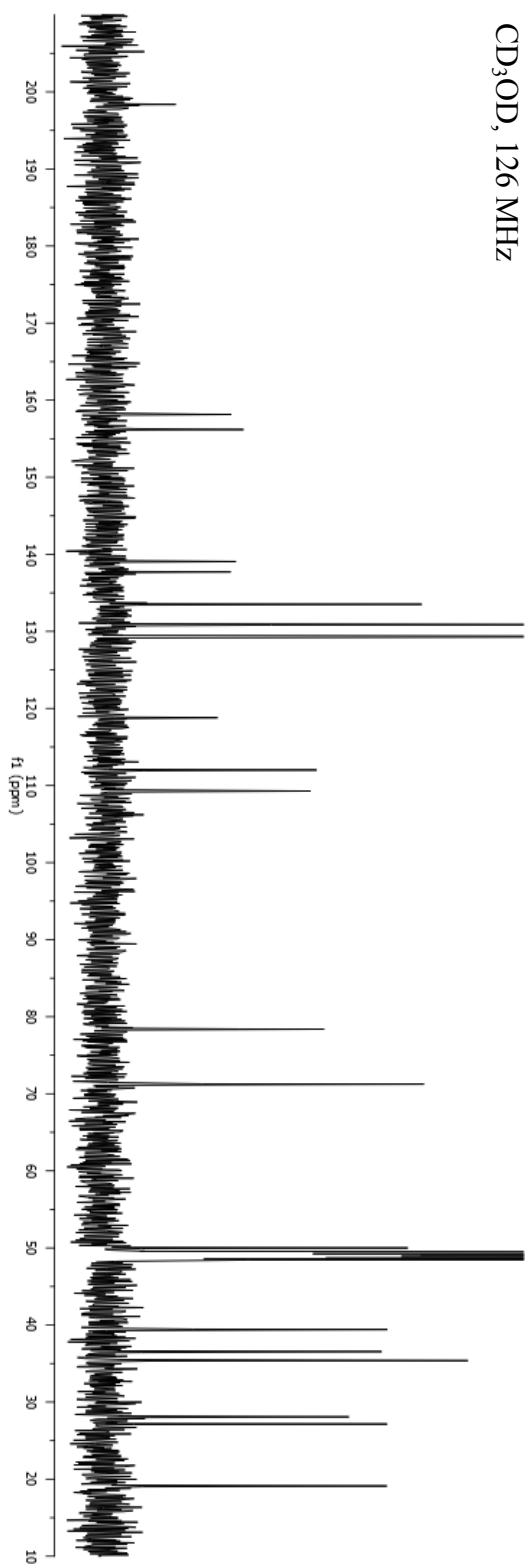
CD<sub>3</sub>OD, 500 MHz



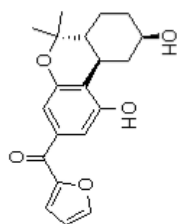
**148**



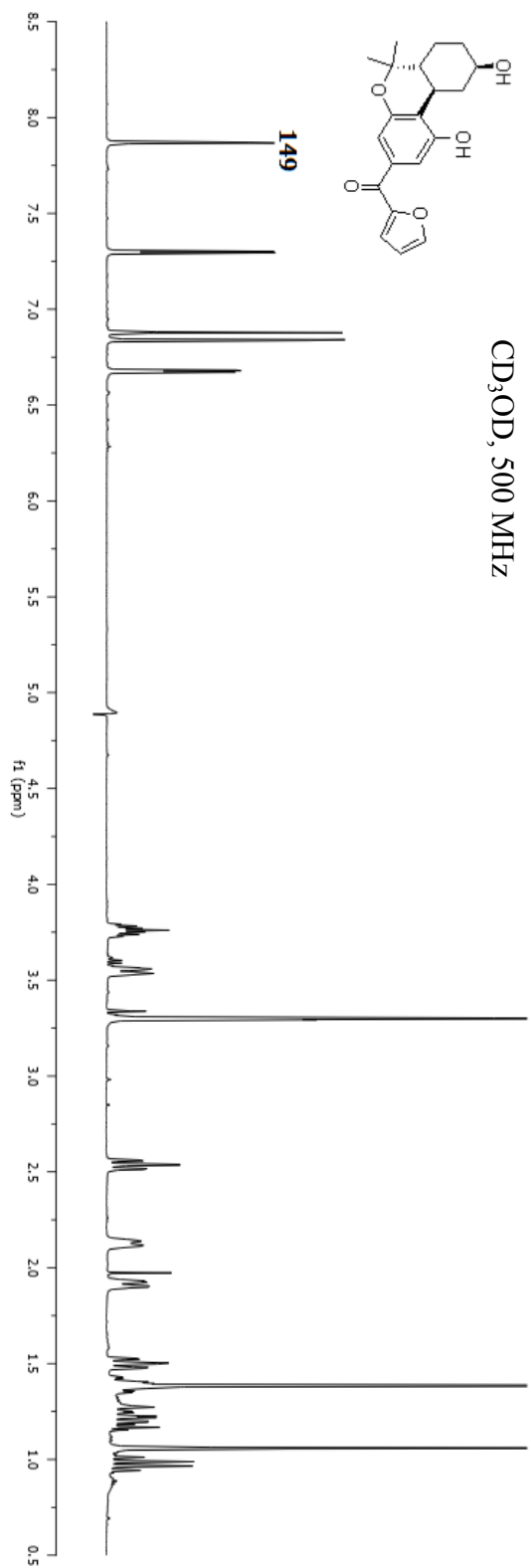
CD<sub>3</sub>OD, 126 MHz



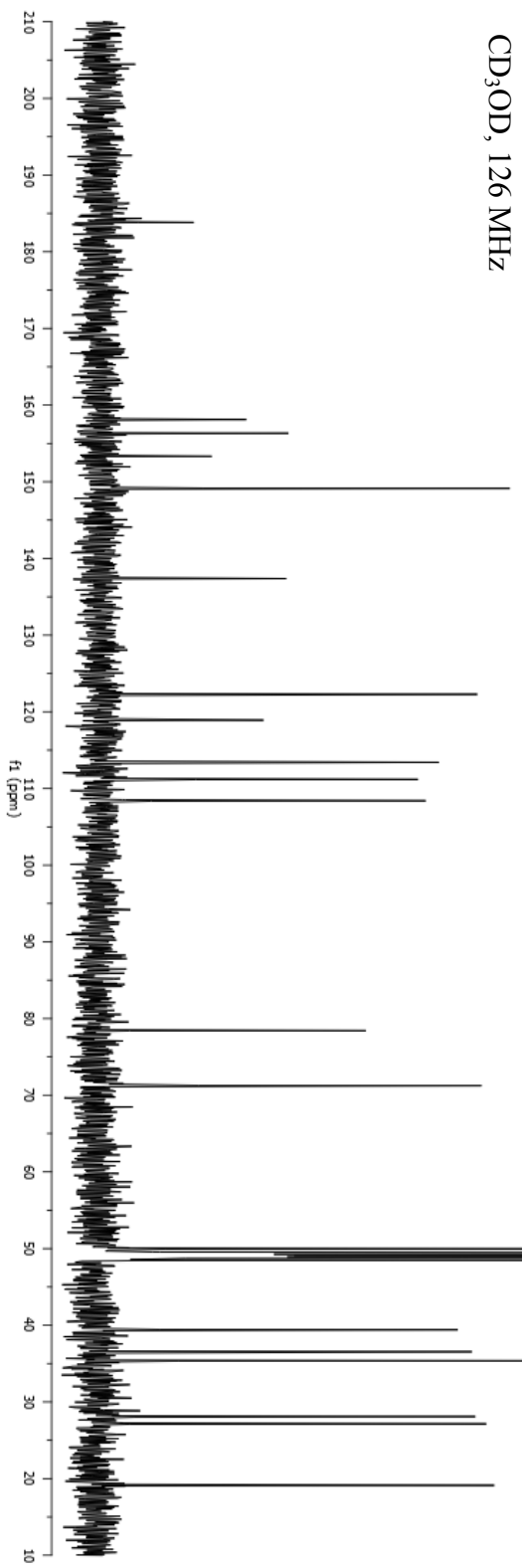
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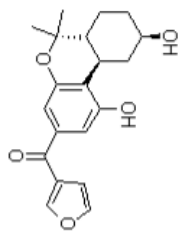
**149**



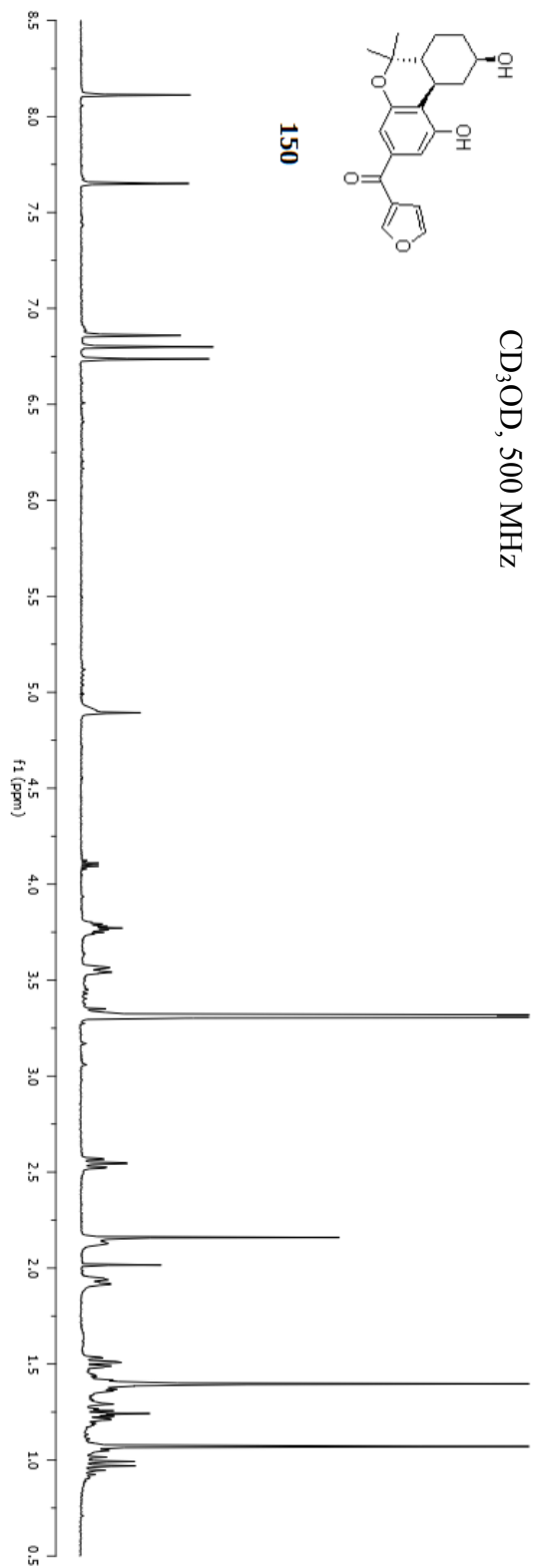
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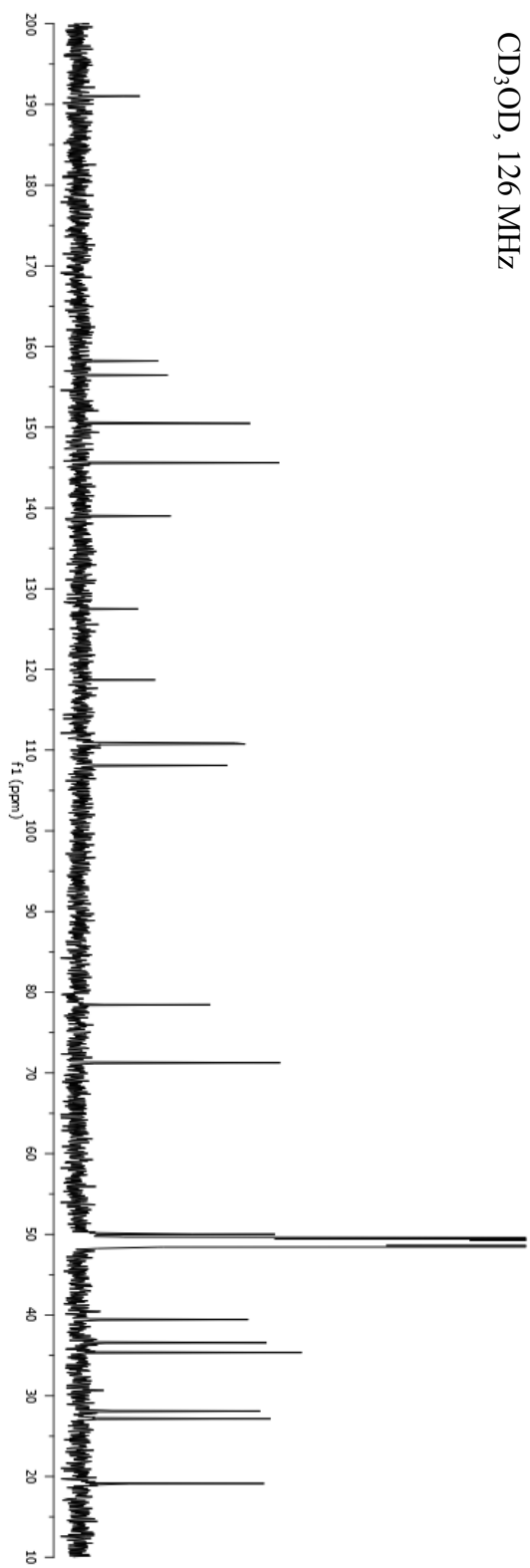
CD<sub>3</sub>OD, 500 MHz



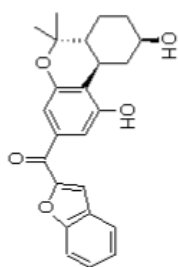
**150**



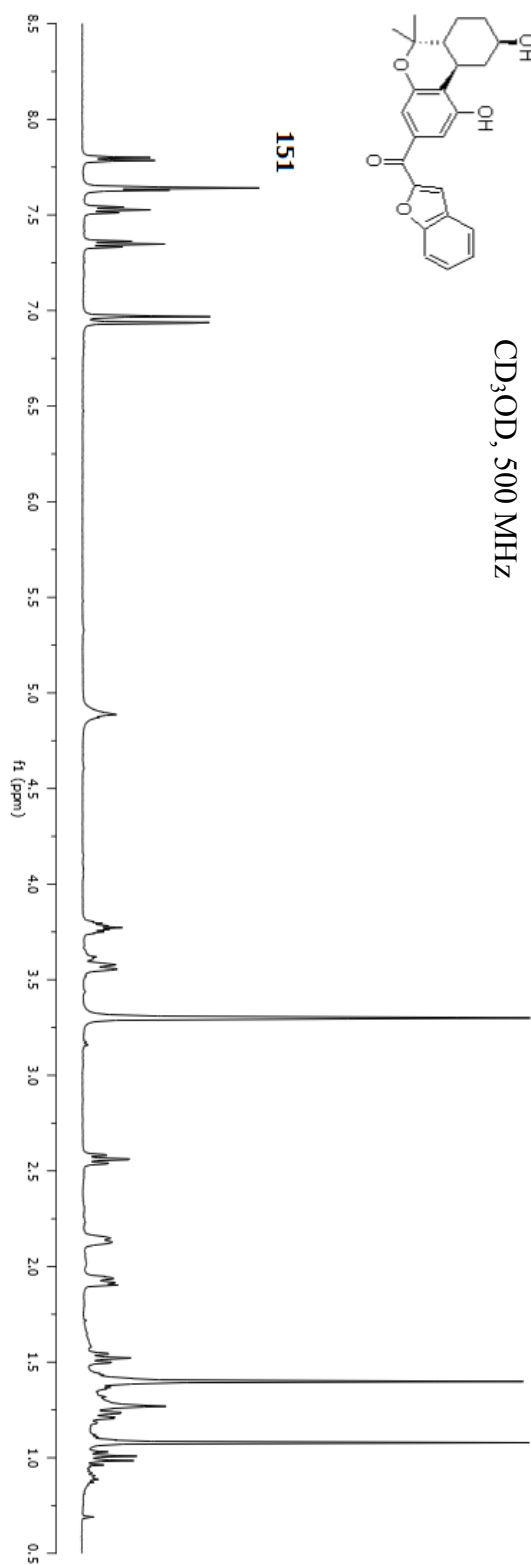
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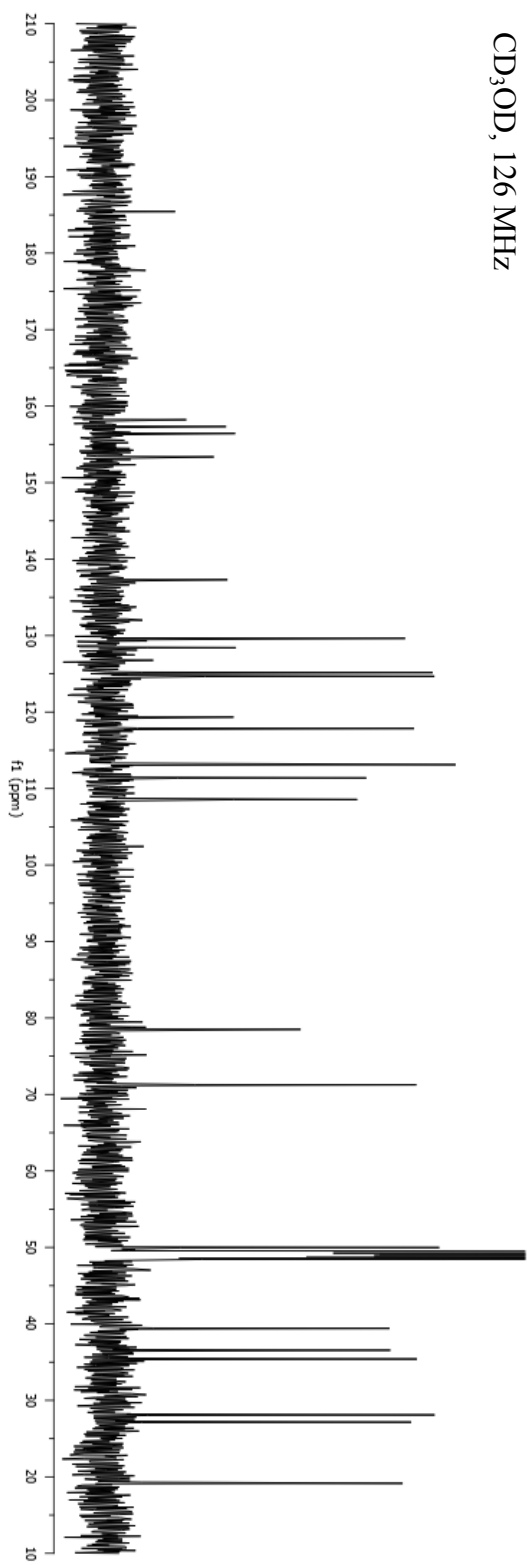
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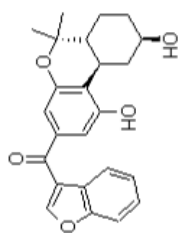
151



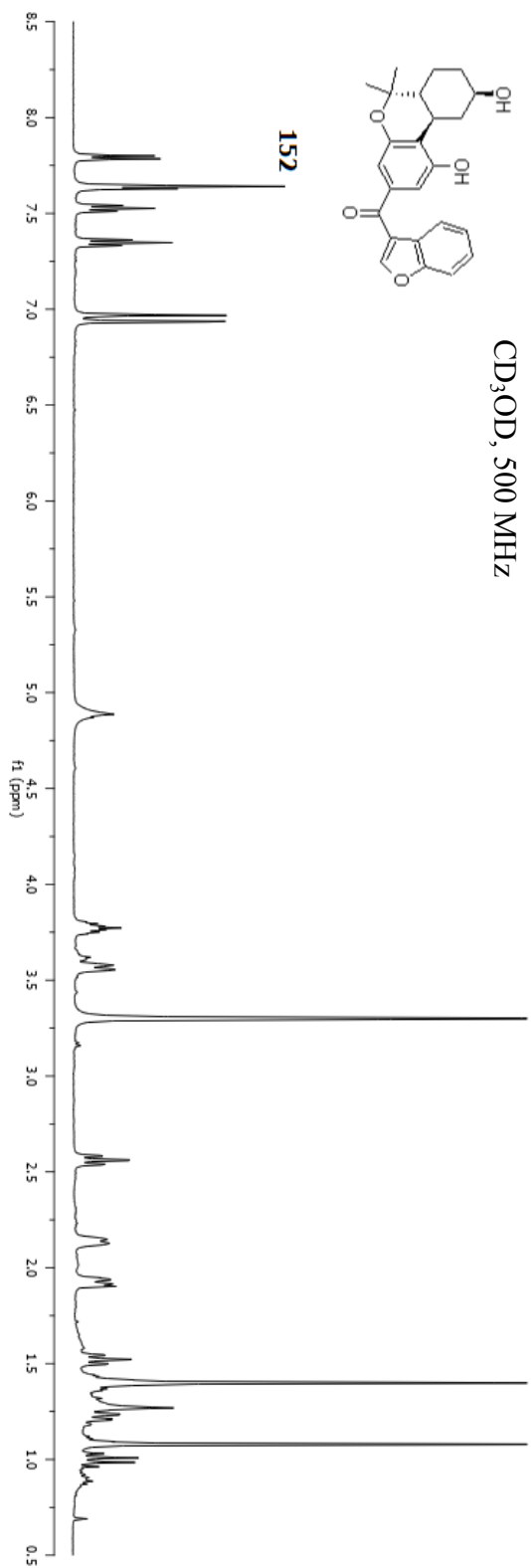
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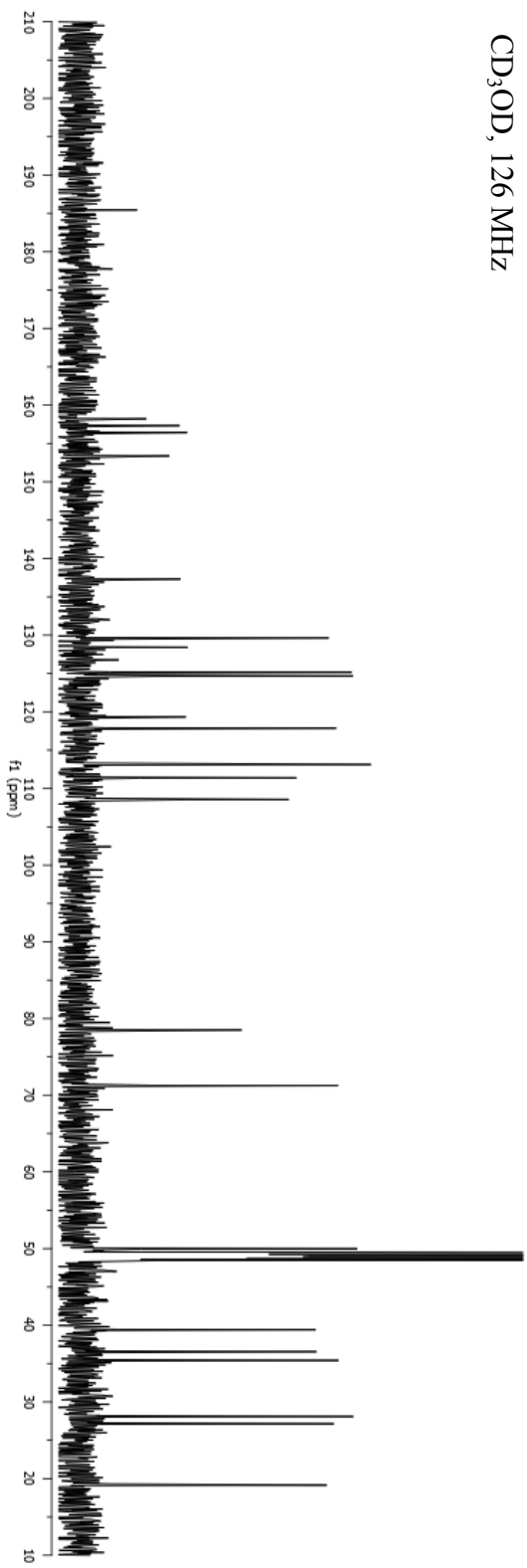
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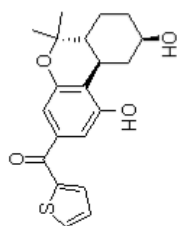
152



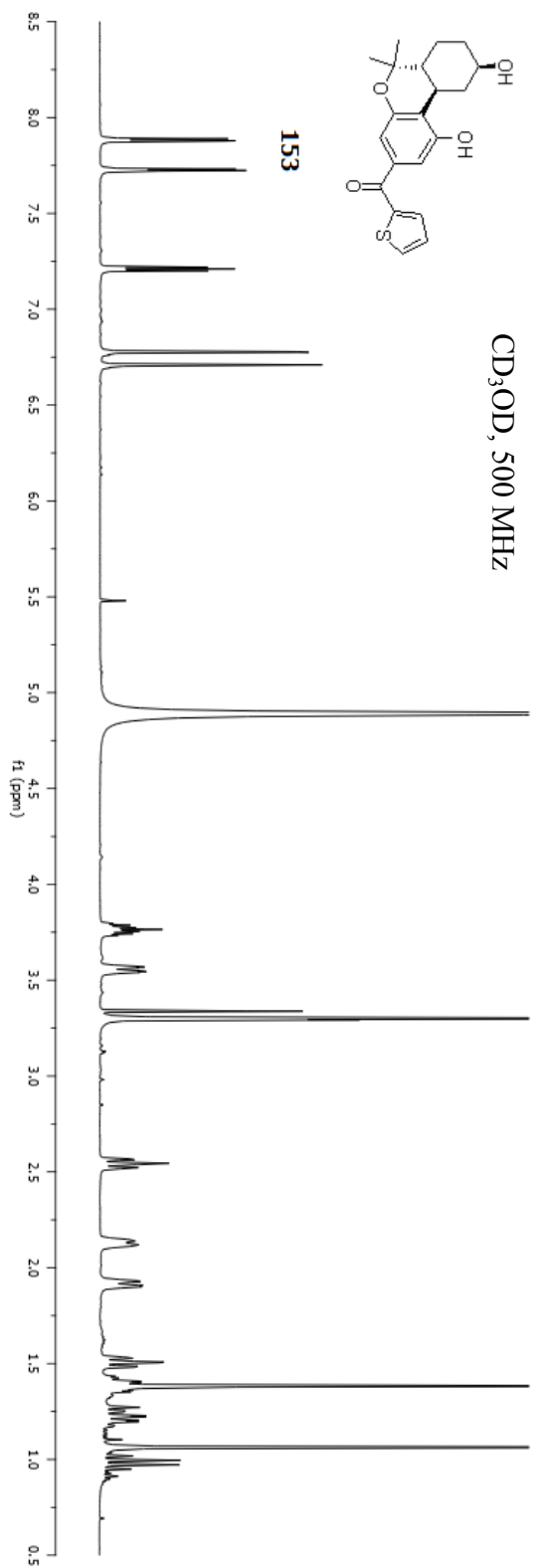
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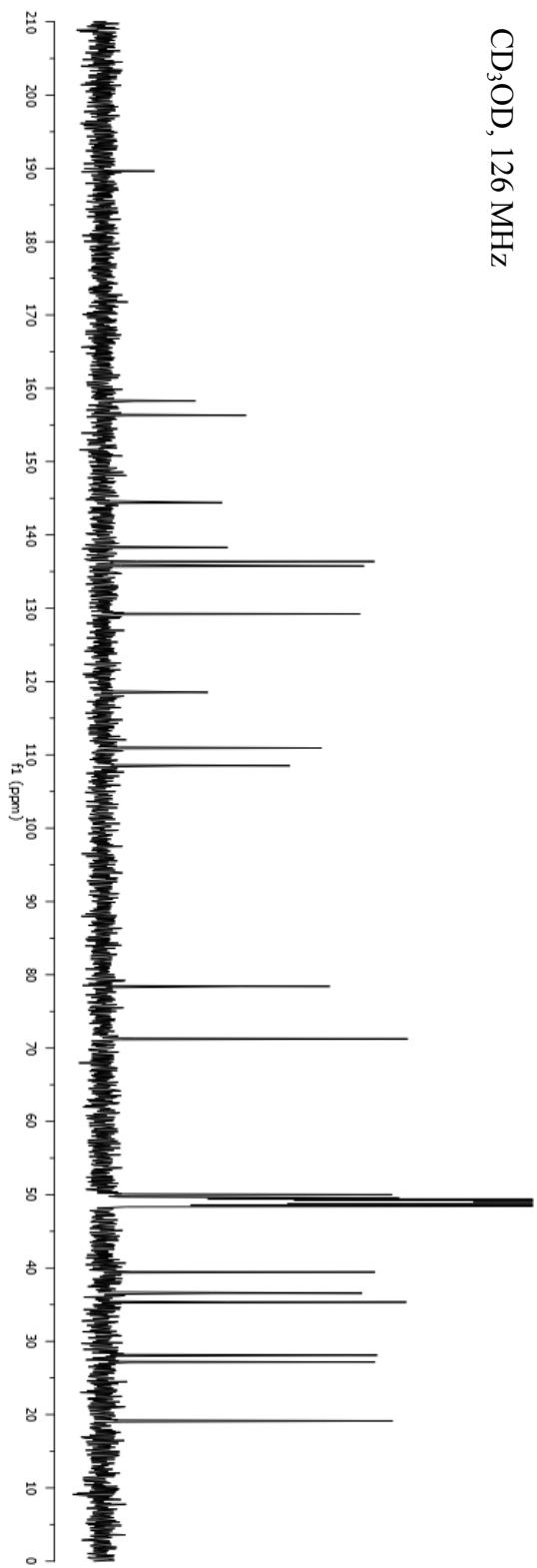
CD<sub>3</sub>OD, 500 MHz



**153**

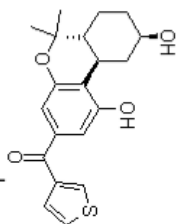


CD<sub>3</sub>OD, 126 MHz

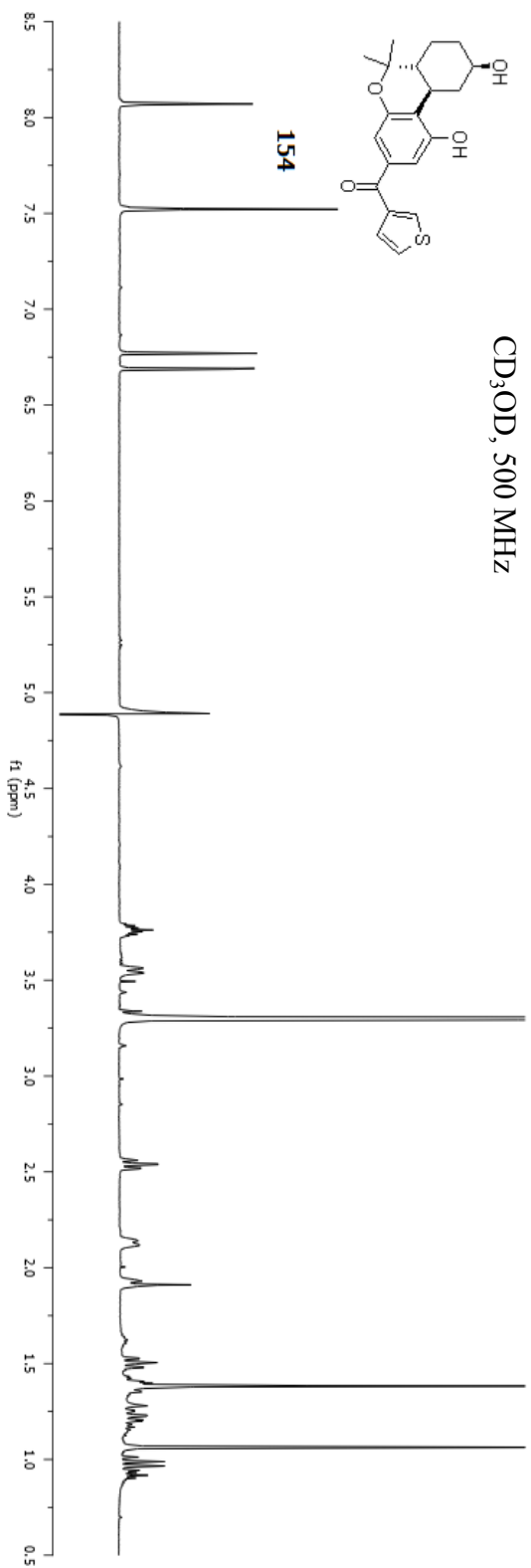




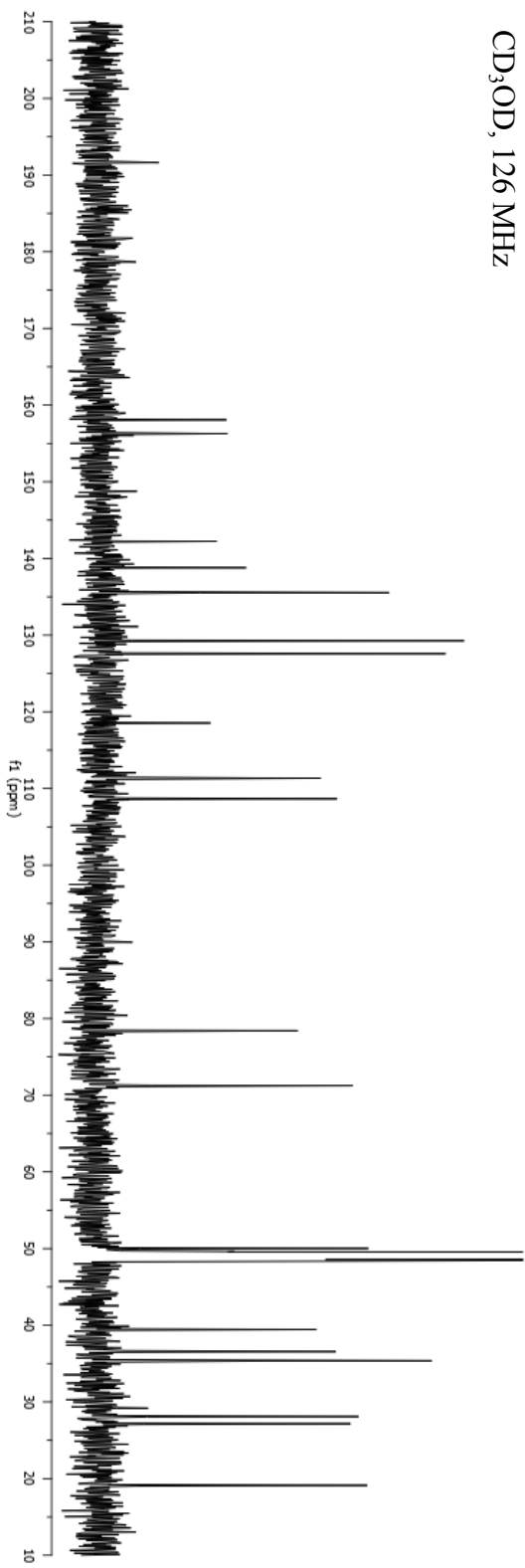
CD<sub>3</sub>OD, 500 MHz



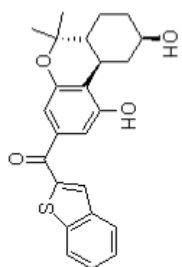
**154**



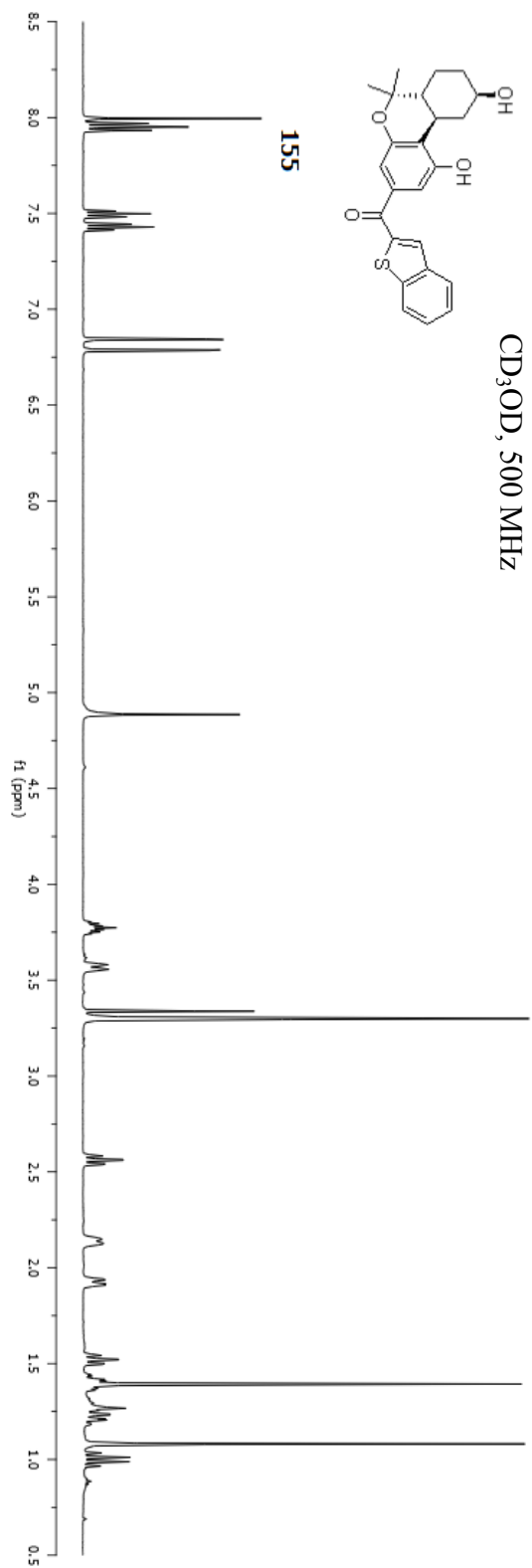
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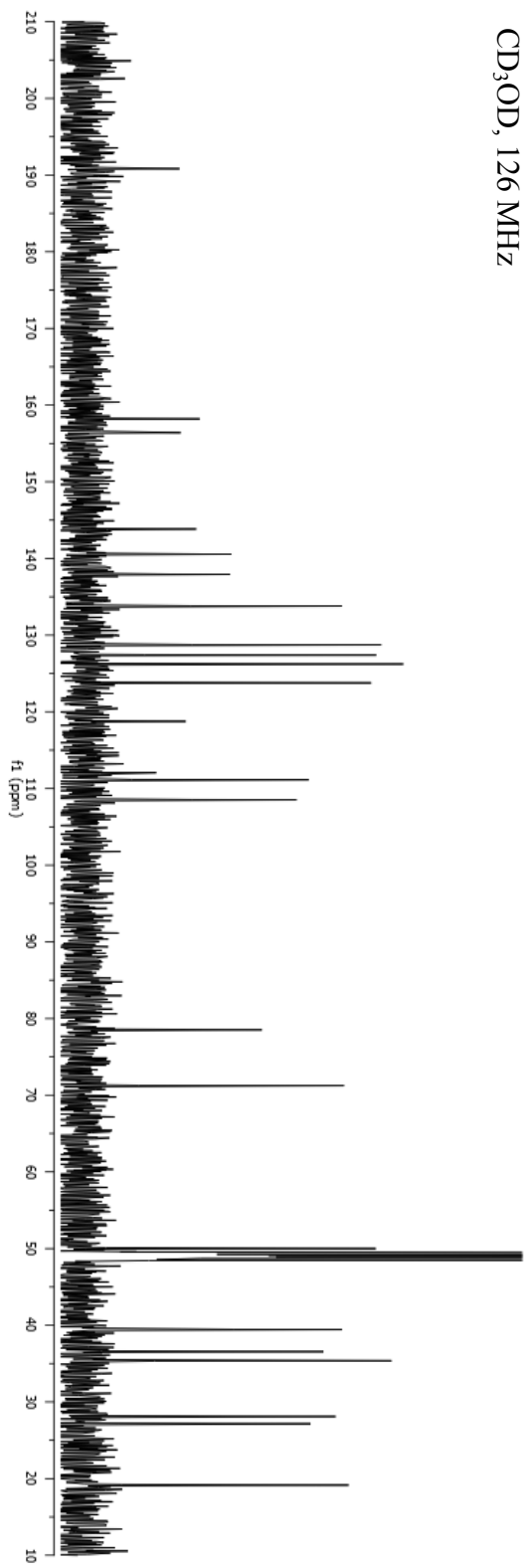
CD<sub>3</sub>OD, 500 MHz



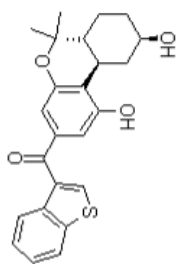
**155**



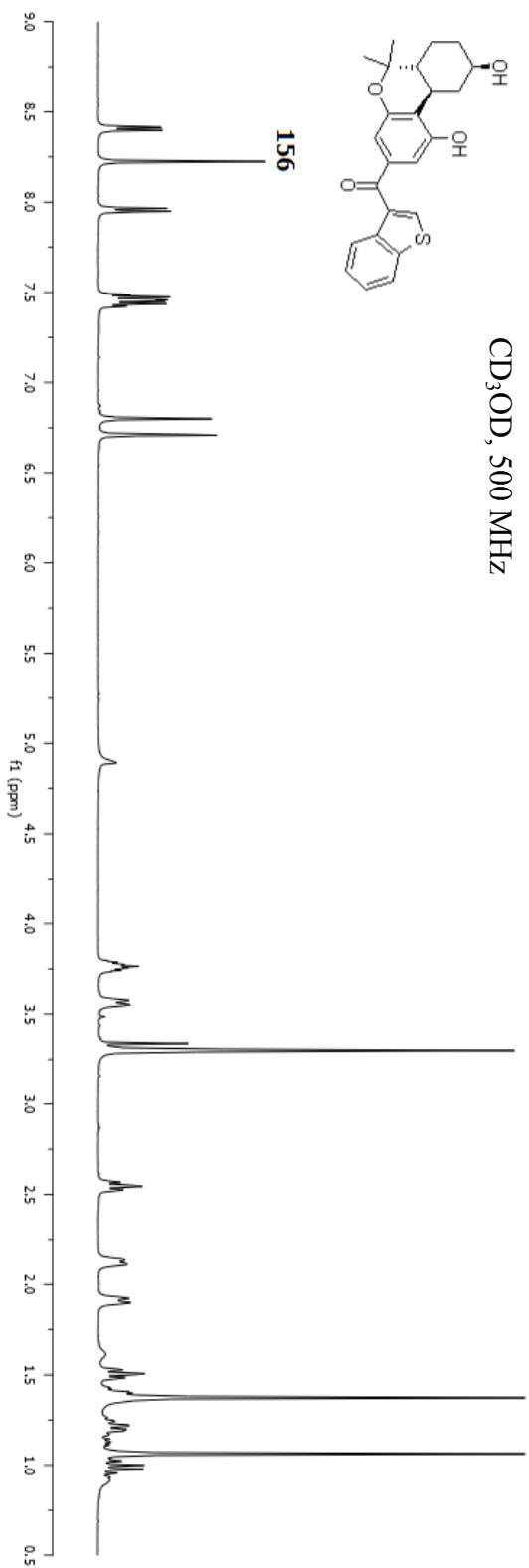
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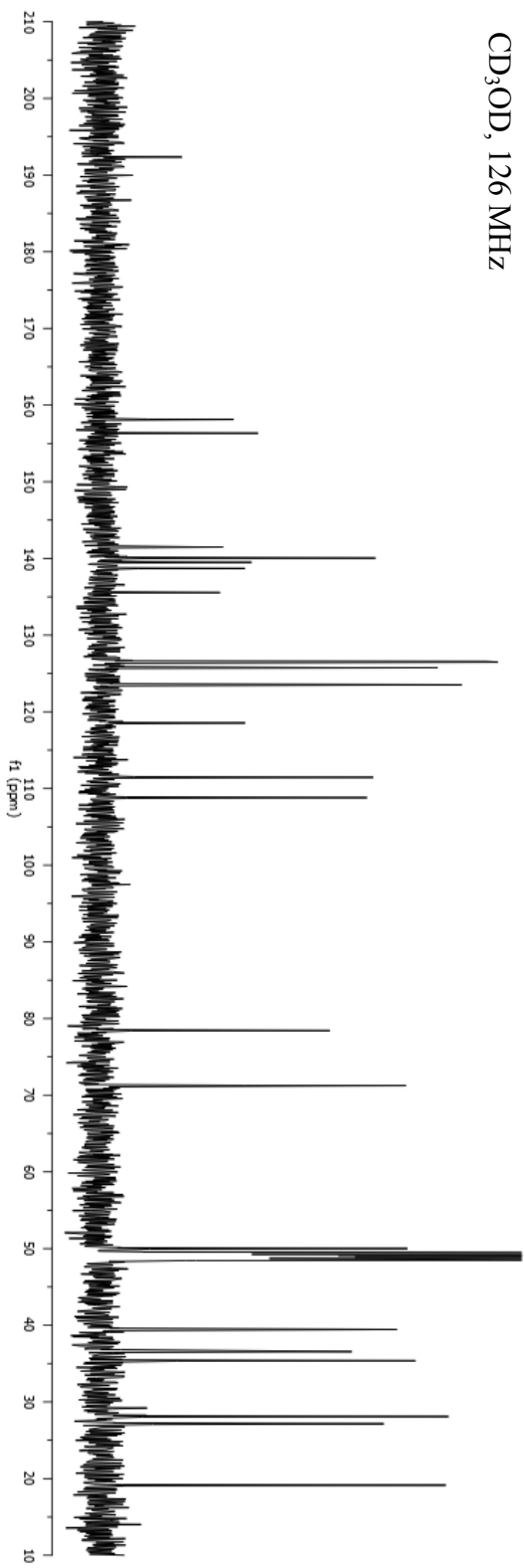
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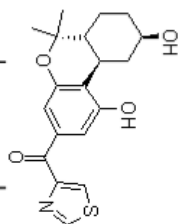
**156**



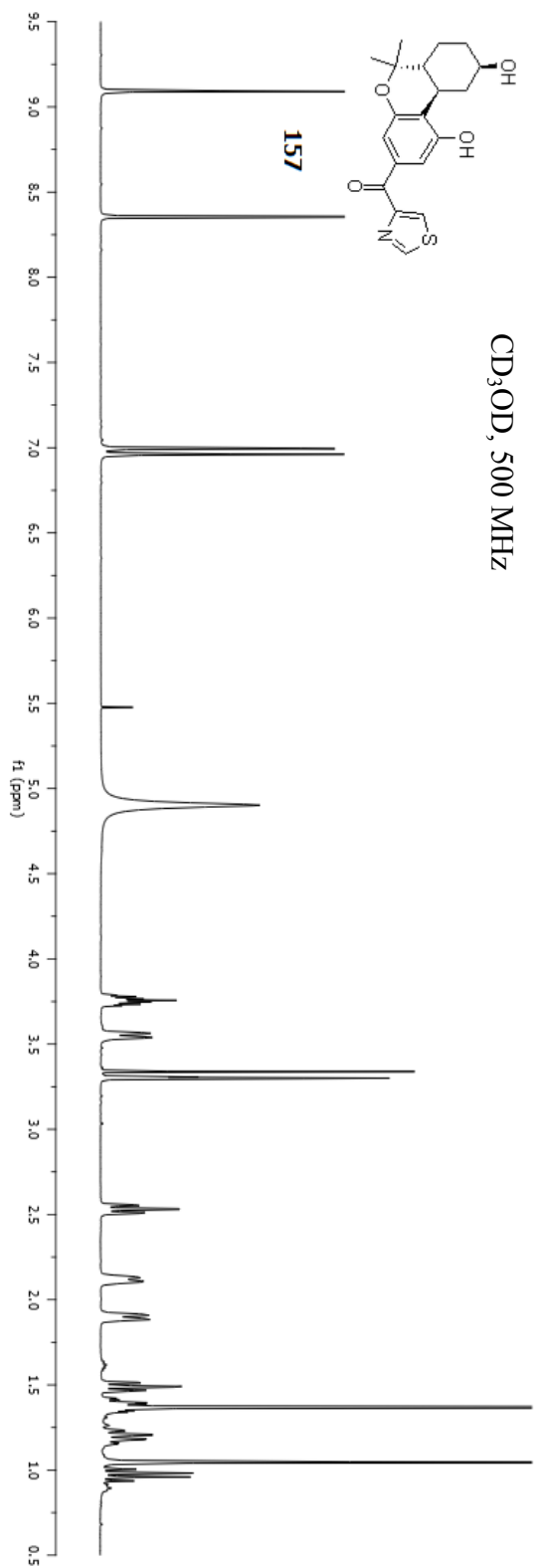
CD<sub>3</sub>OD, 126 MHz



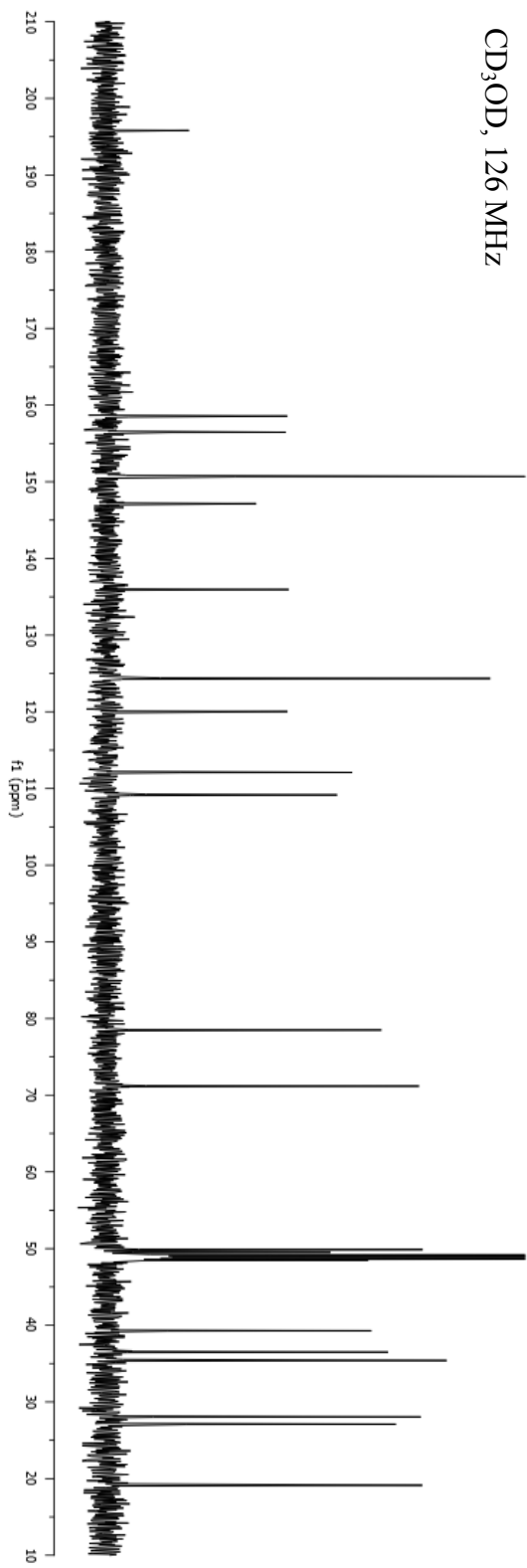
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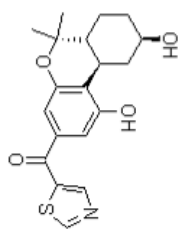
**157**



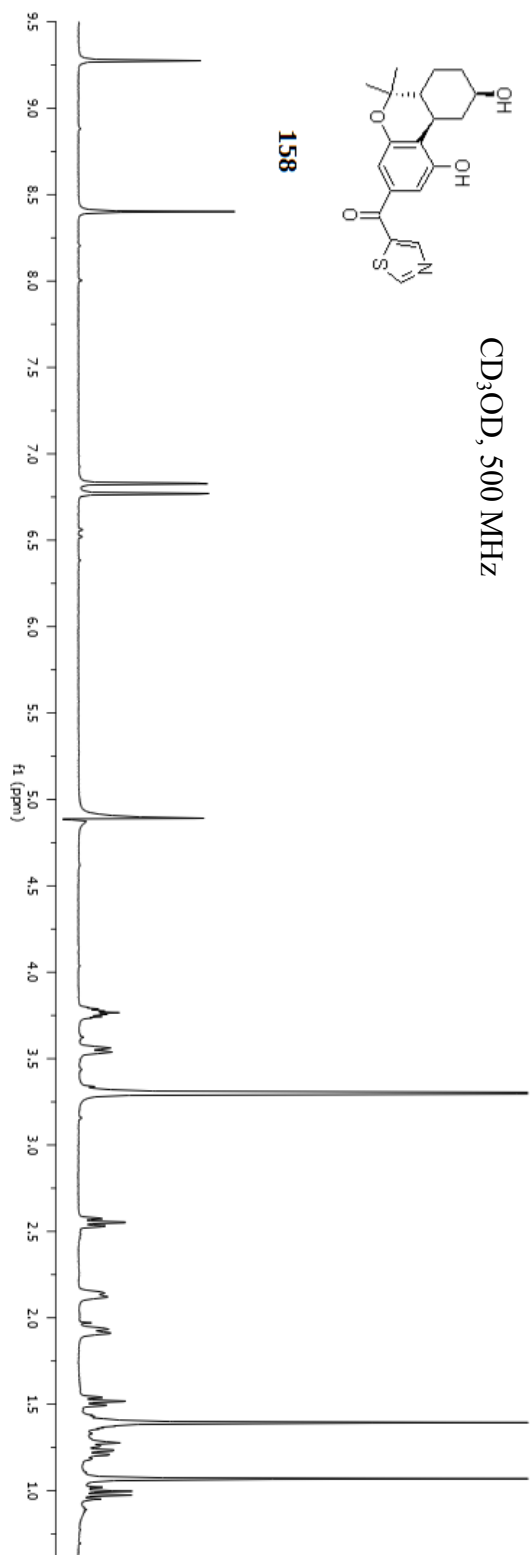
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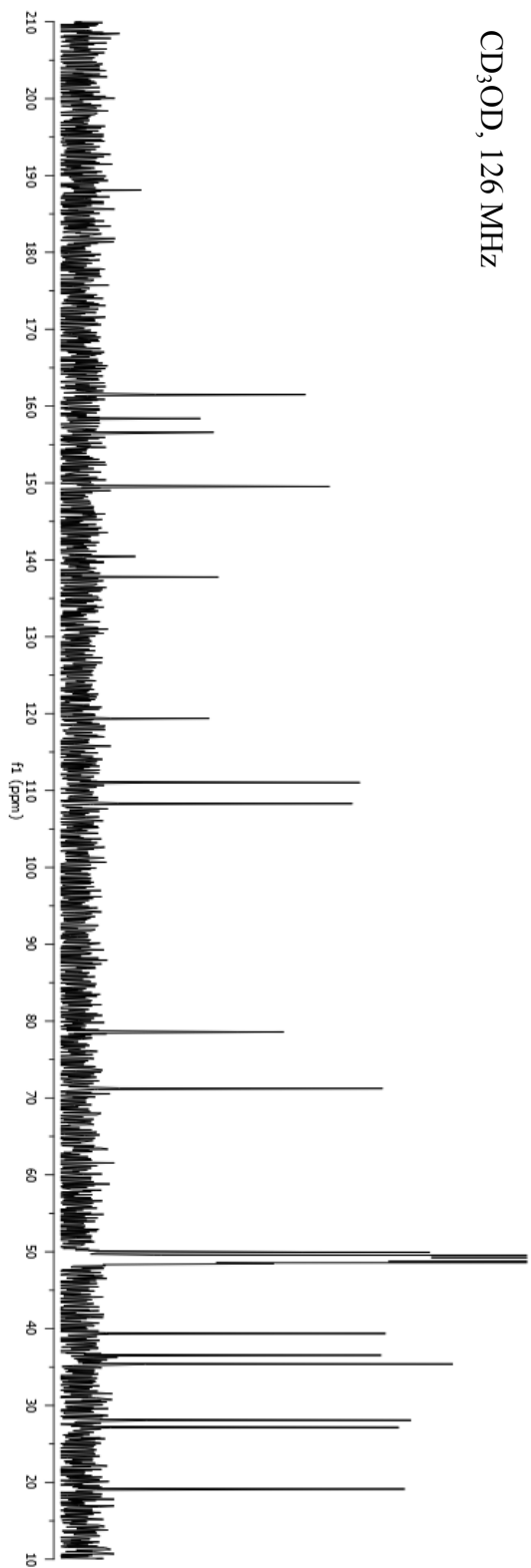
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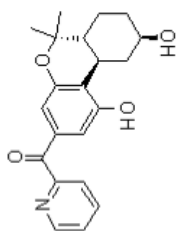
**158**



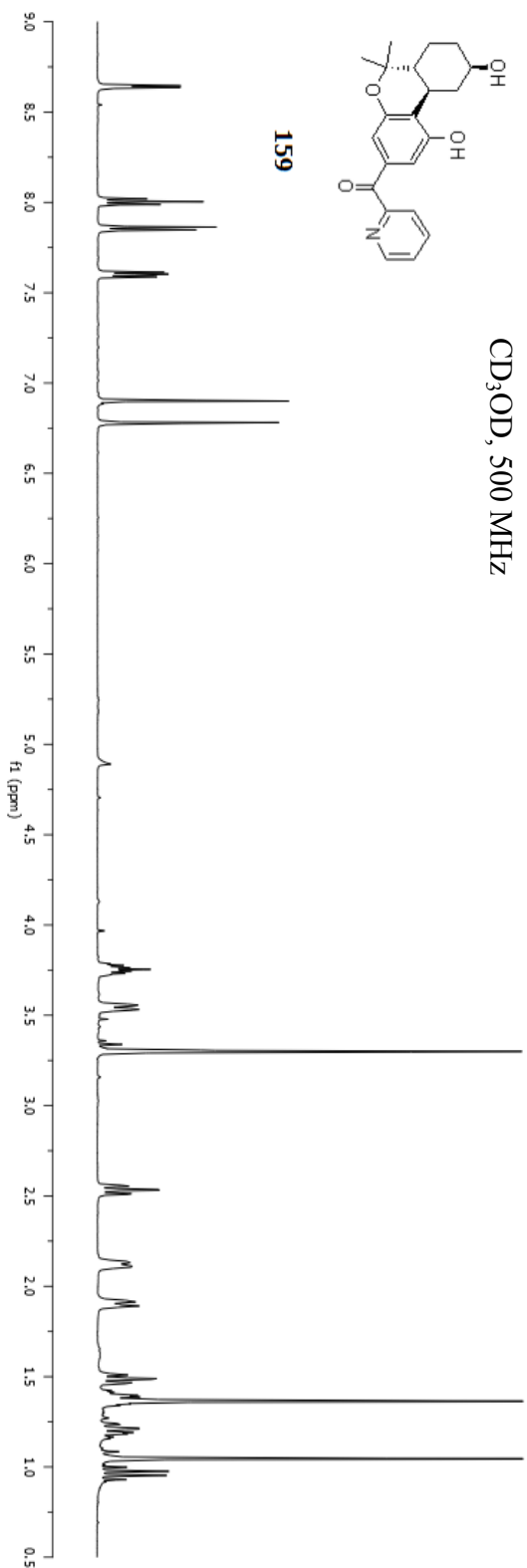
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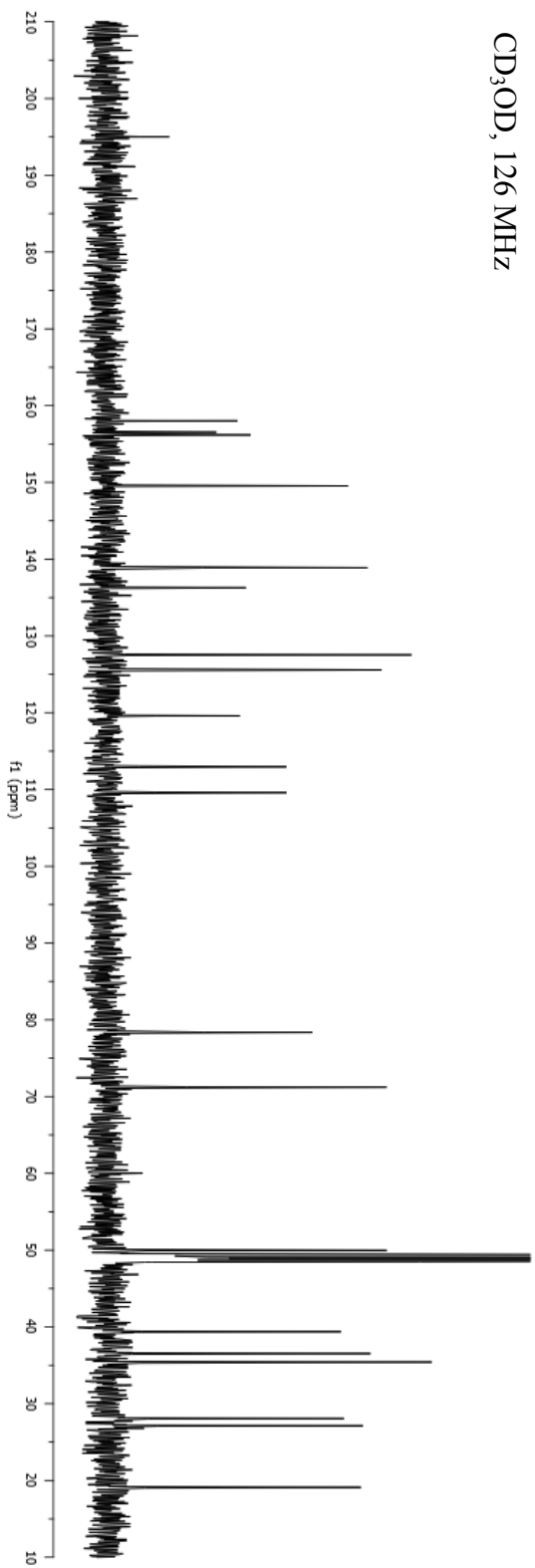
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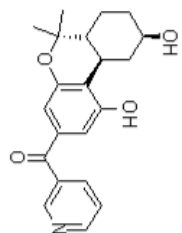
**159**



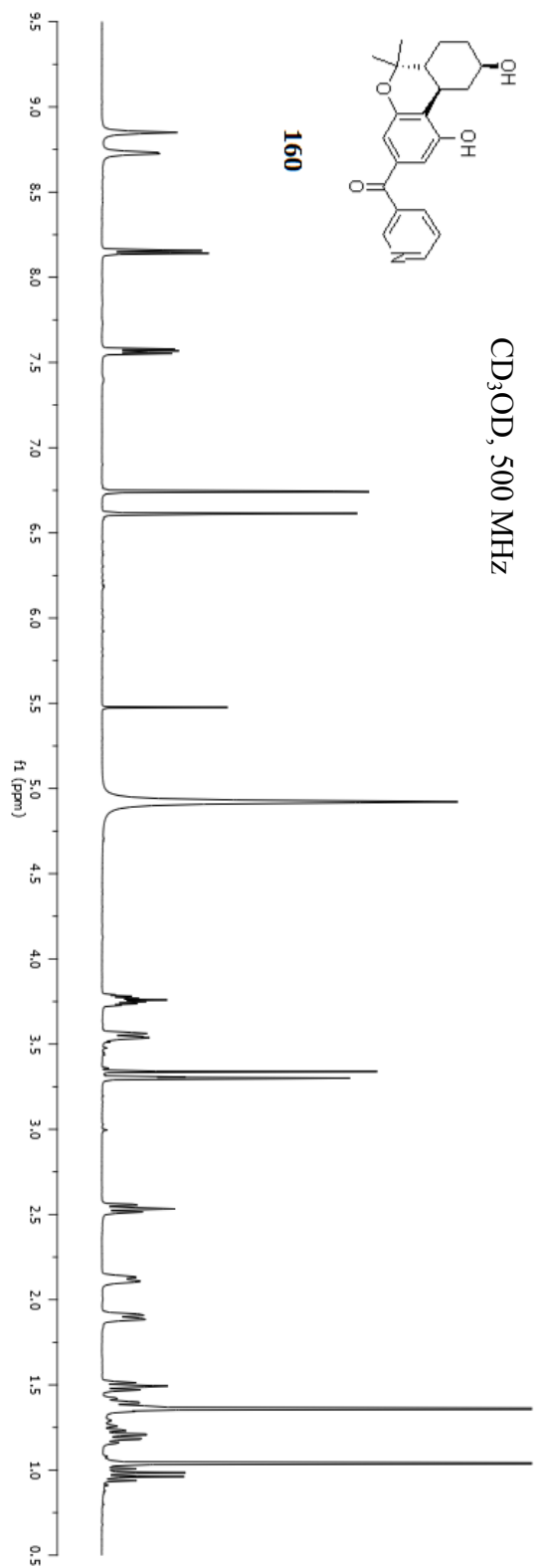
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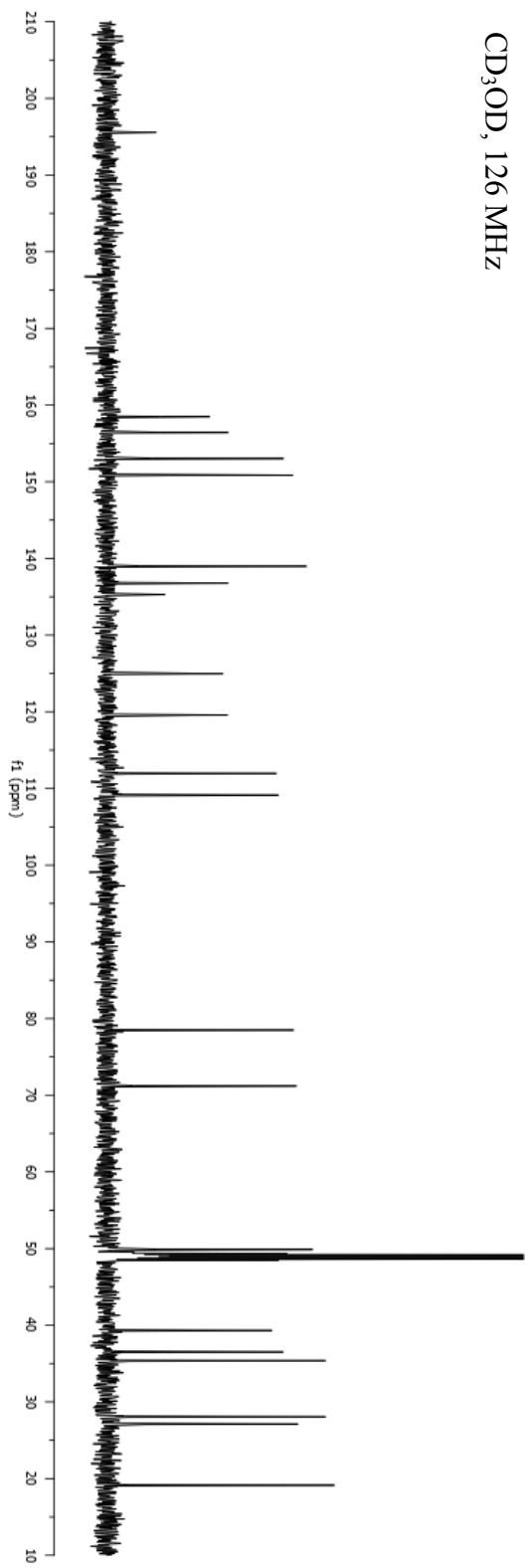
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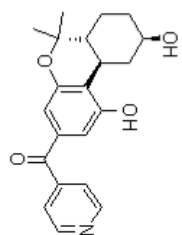
**160**



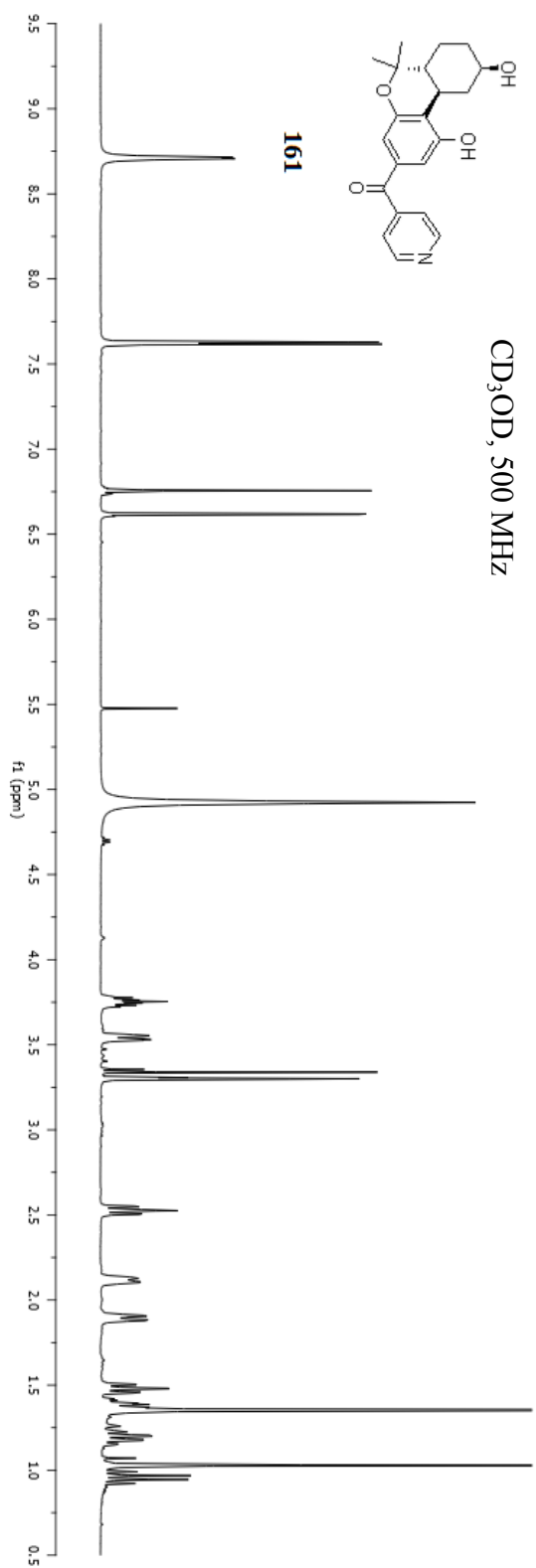
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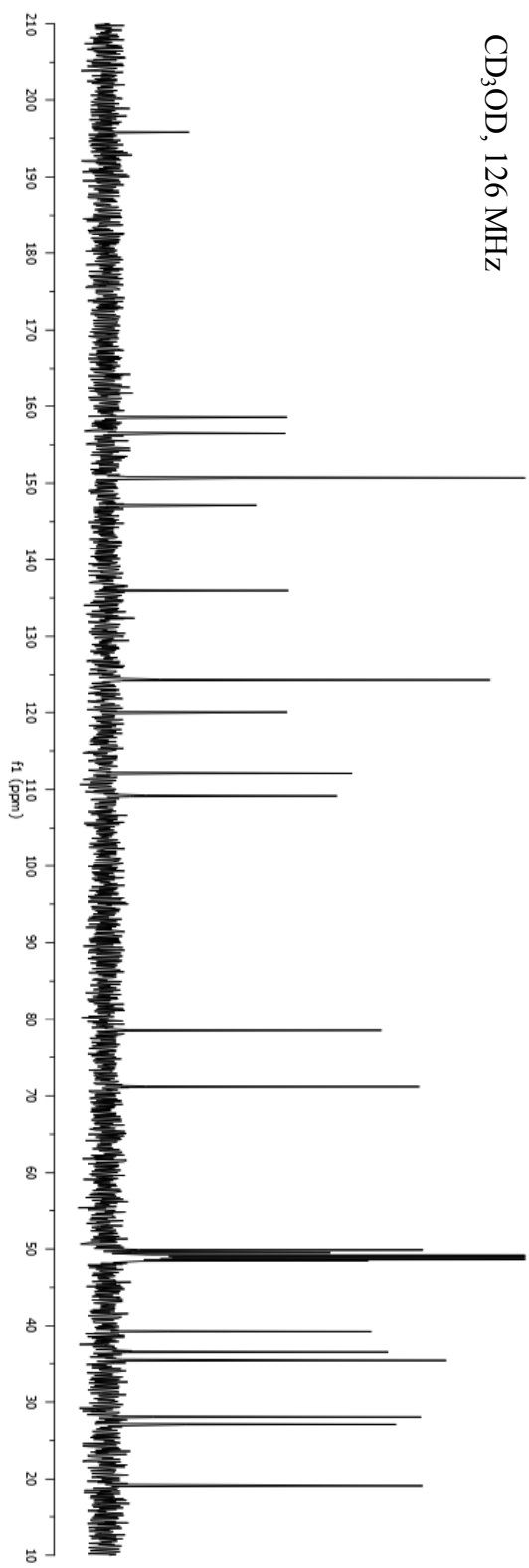
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**161**

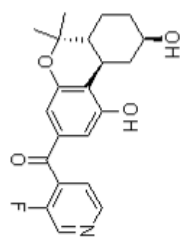


CD<sub>3</sub>OD, 126 MHz

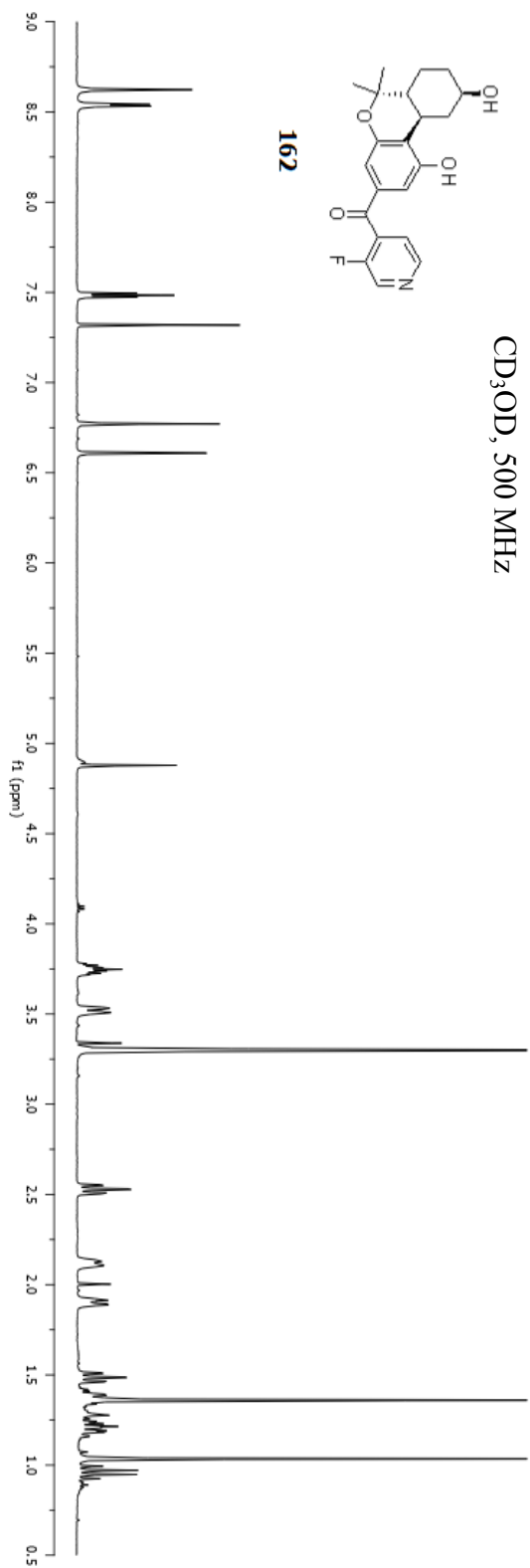




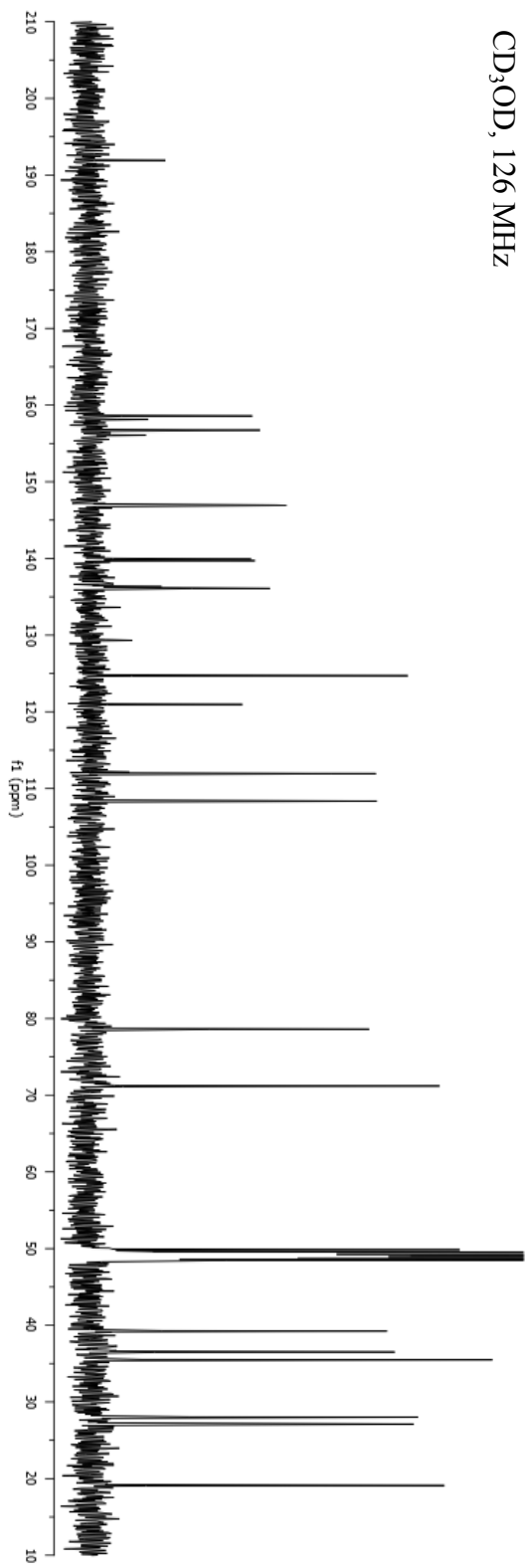
CD<sub>3</sub>OD, 500 MHz



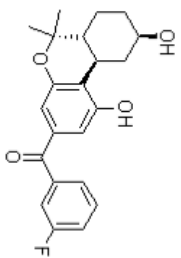
**162**



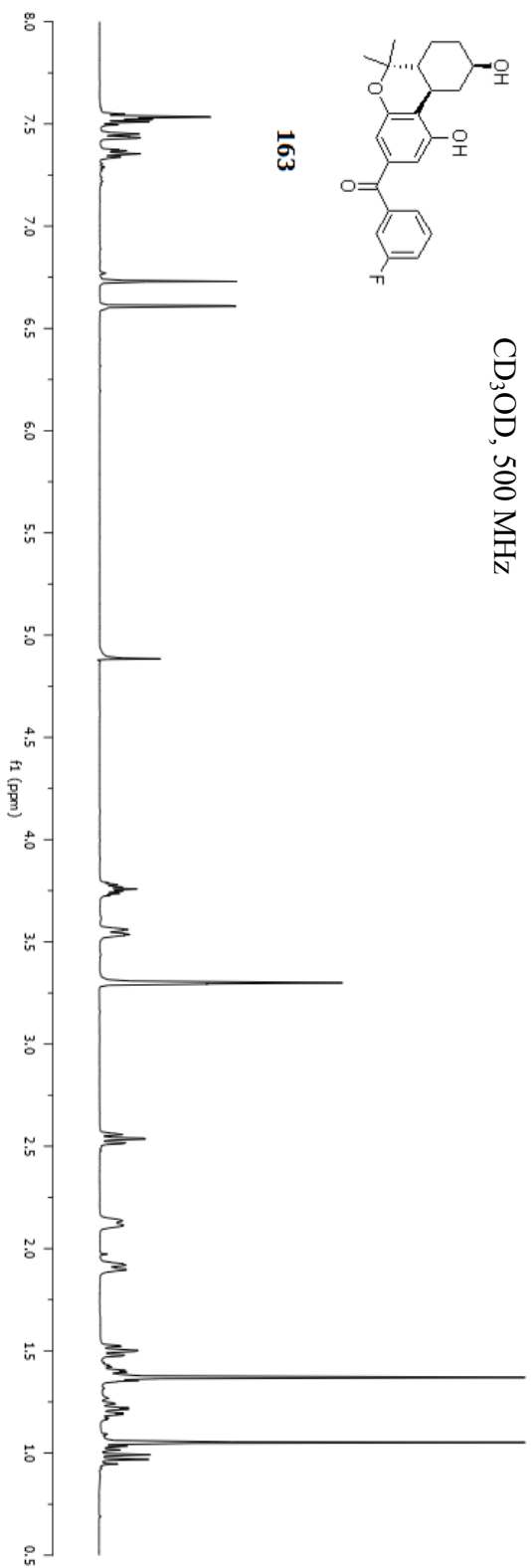
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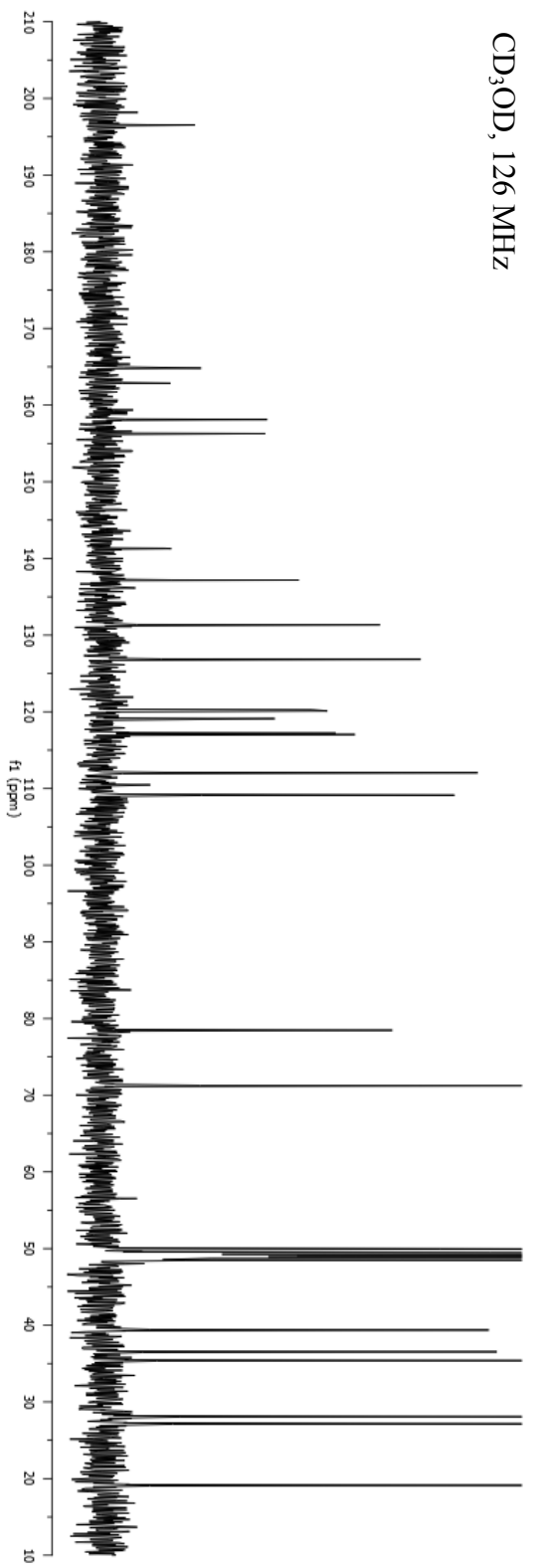
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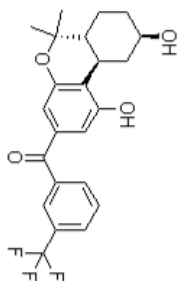
**163**



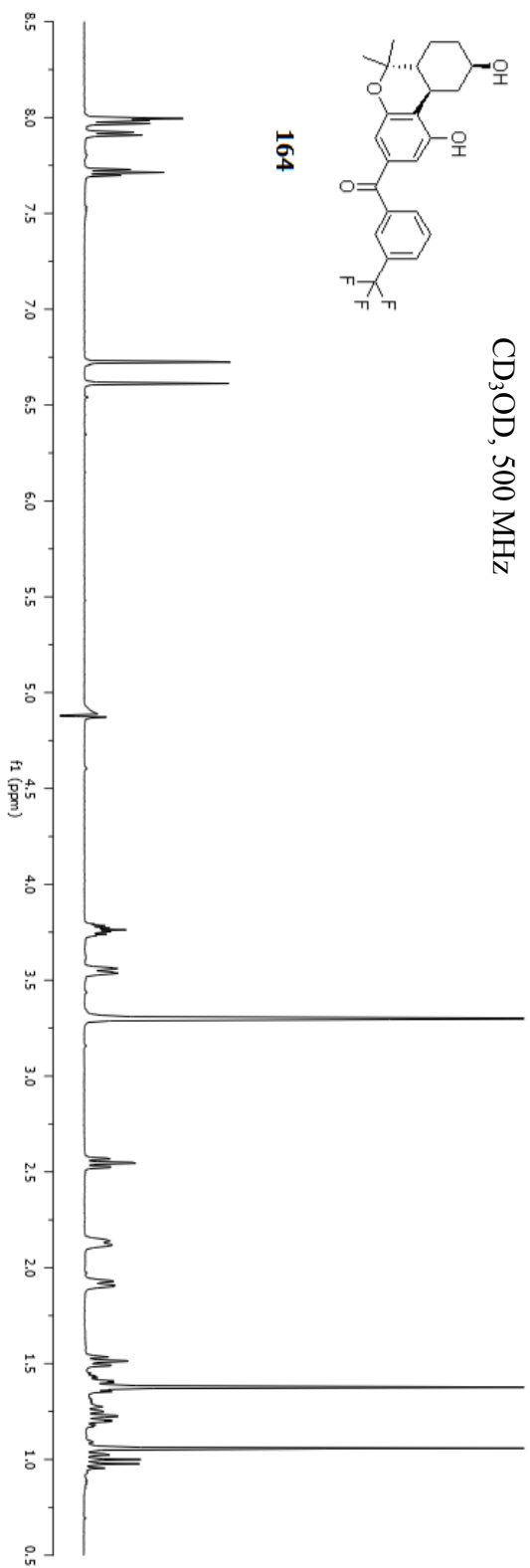
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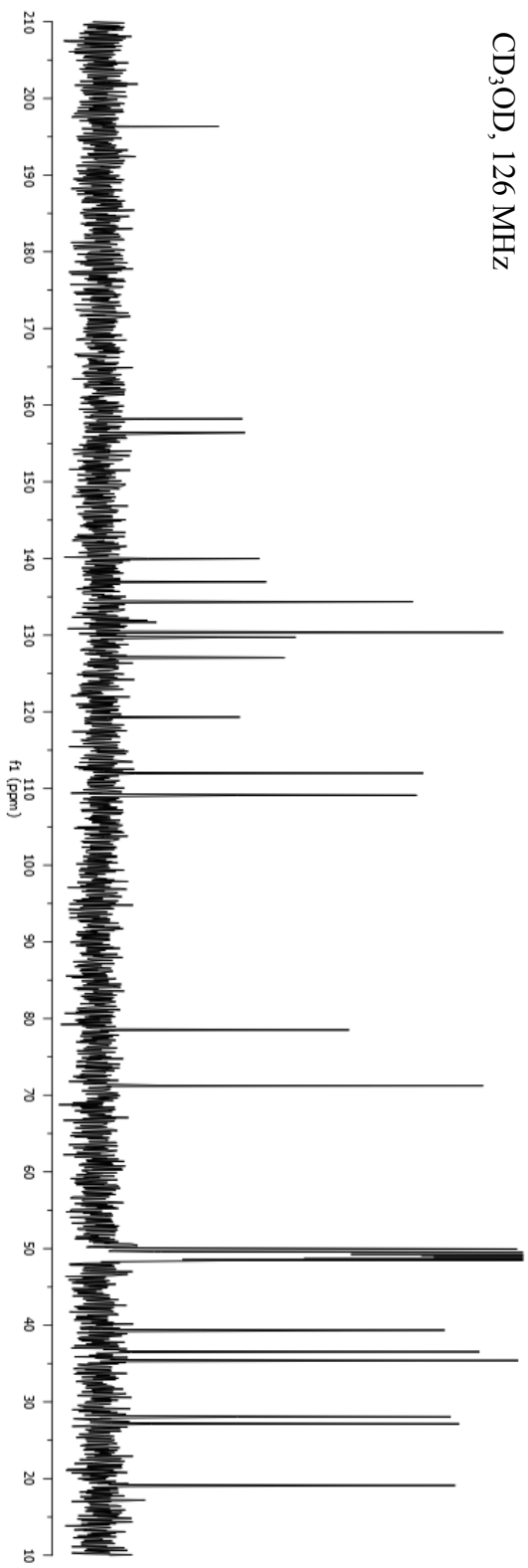
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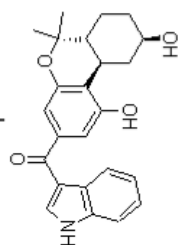
**164**



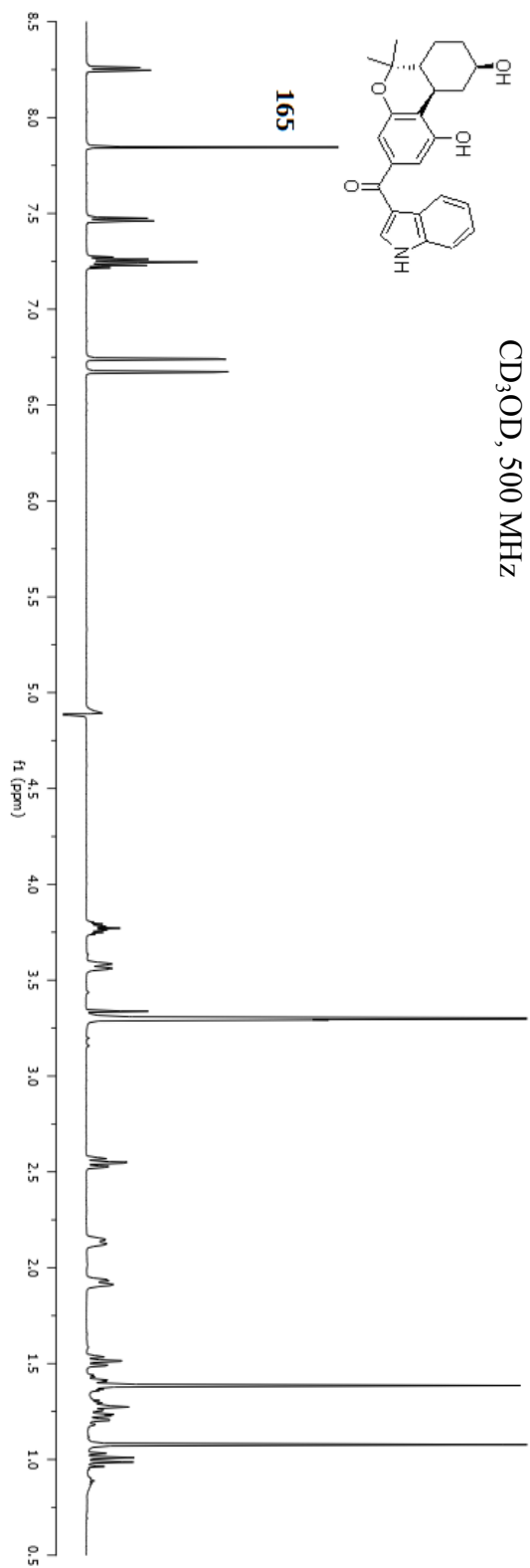
CD<sub>3</sub>OD, 126 MHz



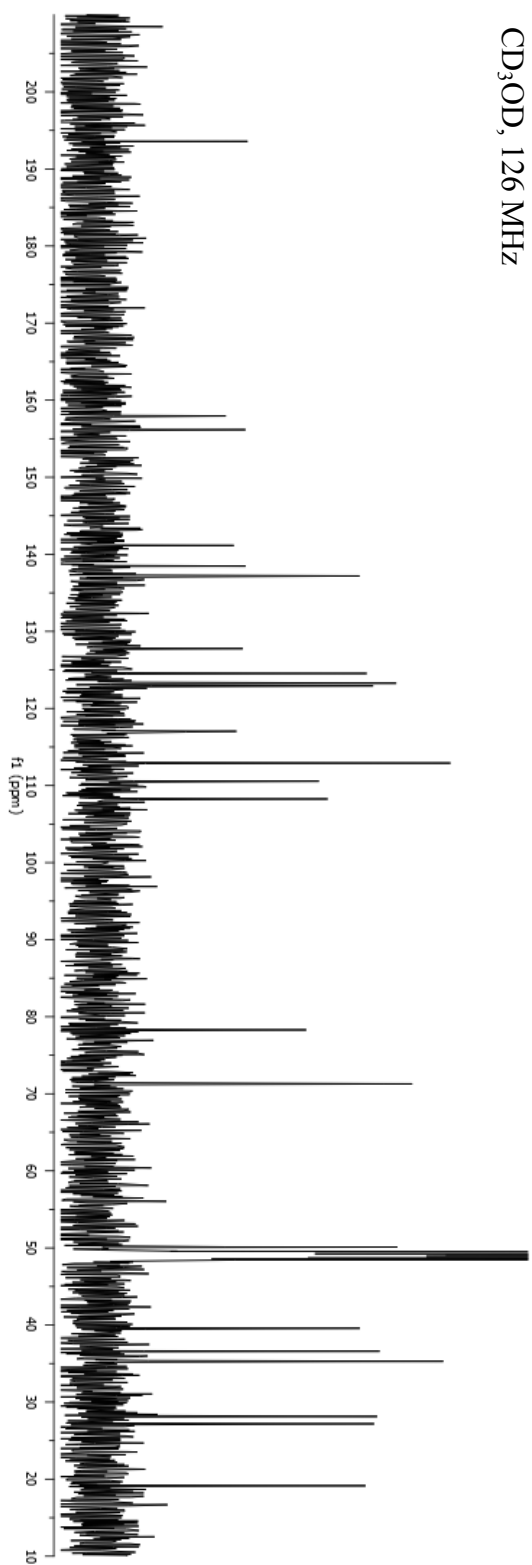
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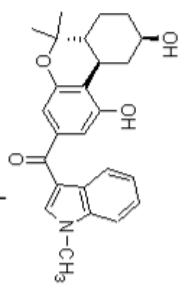
165



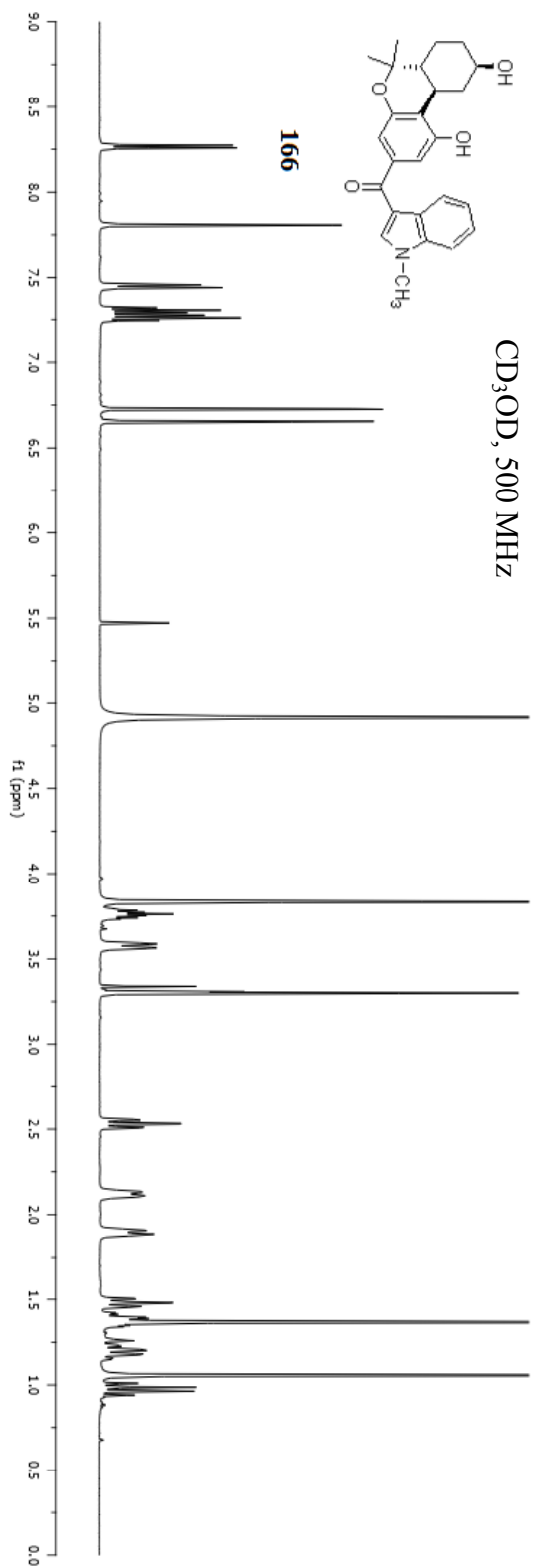
CD<sub>3</sub>OD, 126 MHz



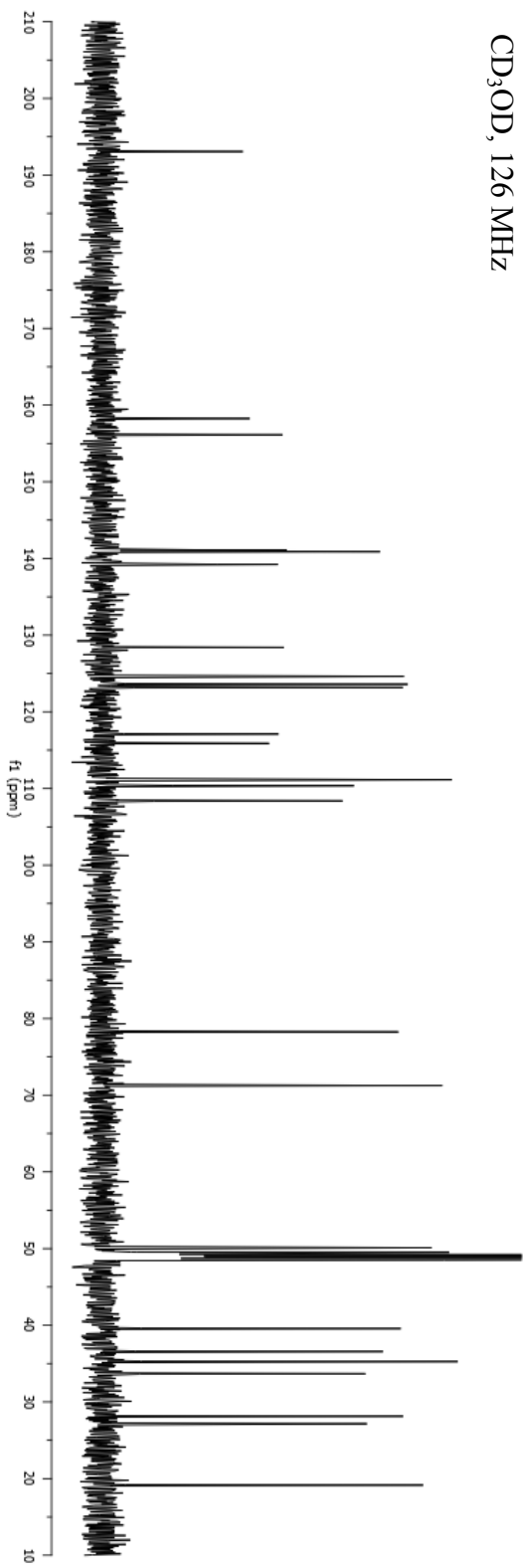
CD<sub>3</sub>OD, 500 MHz



**166**



CD<sub>3</sub>OD, 126 MHz



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